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# Evaluation of the Methods of Treatment of Essential Hypertension

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WHILE it is generally accepted that about 95 per cent of all hypertension is of the essential type, there still is no agreement regarding the etiology and the nature of the condition, despite the huge amount of study and writing on the subject.[1] The types caused by renal, humoral, neurogenic and a few other causes have been fairly well delineated. The old question regarding the relationship of essential hypertension to arteriosclerosis still remains unanswered. This failure does not indicate that no progress has been made in our knowledge of hypertension itself. Intensive research during the past five years has resulted in the discovery of some potent drugs for lowering blood pressure. While no ideal agent has been found to be effective in all cases, several drugs are considered useful therapeutically in some instances.

It is not our purpose in evaluating the modern management of hypertension to consider only drugs and their actions. Other methods of treatment, although well known, seem to have been half forgotten and neglected. The failure of physicians to take adequate time to discuss fully the significance of the individual's problems, the decreasing emphasis placed on the patient's habits, and the diminishing role of the diet in the control of hypertension are to be deplored.

Newer drugs have been used too promiscuously and exclusively in the management of hypertension, although they have been helpful therapeutically in some but not all cases. It appears to be forgotten that many hypertensive patients require little or no treatment and live satisfactorily for many years. Some physicians have become so drug-conscious that

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every patient with any degree or type of high blood pressure receives so-called "benefits" of hypotensive drugs, but in some instances instead of being beneficial the results are detrimental. The ecstasy with which these drugs are reported, sold and used requires considerable modification. Having lived through a period of therapeutic nihilism, we know the "do nothing" policy is also not acceptable, but there must be a middle course between the extremes of the old and the excesses of the new.

The new drugs alter one factor of the disorder, namely, the high blood pressure itself, and generally fail, as far as we know, to modify some essential conditions which are a part of the disease. The relation of high blood pressure to the metabolic, humoral and vascular changes associated with it is one of the disputed questions of the day. Some recent articles discuss such topics as "Hypertensive disease without hypertension" in which the control of the blood pressure itself did not control the associated changes.[2] Many of the newer articles corroborate older ideas which have been known for many years—that the height of the blood pressure itself is not the paramount issue in treatment of the disorder. The level of the blood pressure may have less significance than usually believed.[3]

The present-day concept of essential hypertension assumes that it is a specific disease entity and that it has a specific etiology, the nature of which has not been determined. This means that the difference between normal blood pressure and essential hypertension is one of kind and not of degree. Pickering[4] disagrees with this and believes that the fundamental assumption of a qualitative difference between essential hypertension and normal blood pressure is, if not wrong, at least without substantial justification. His own concept is that the difference is proved quantitatively. However, this is a problem with which to cope at another time.

### *Classification of Hypertension*

With these preliminary remarks, a discussion of a satisfactory working classification of hypertension is necessary. It would be a platitude to say that this is quite important in evaluating a patient with high blood pressure. Some patients with high blood pressure need no special treatment at all, others minimal treatment, and still others vigorous therapy. It is essential hypertension in which the hypotensive drugs are most applicable.

As Page[5] points out, elevated blood pressure alone is not the same thing as hypertensive cardiovascular disease. Furthermore, if we use the term "essential hypertension" unguardedly, we may include many different kinds of hypertension with many different mechanisms.

Our classification is given in table 1.

TABLE 1

CLASSIFICATION OF HYPERTENSION

1. *Renal hypertension*
   - Acute glomerulonephritis
   - Lupus erythematosus and/or other collagen diseases
   - Chronic glomerulonephritis
   - Chronic pyelonephritis with contracted kidney
   - Congenital polycystic disease of the kidney
   - Glomerulosclerosis of diabetes (Kimmelstiel-Wilson disease)
   - Obstructive uropathies involving the ureter and kidney (stones and obstructions)
2. *Hypertension of hormonal origin (endocrine)*
   - Pheochromocytoma or other tumors of adrenal gland
   - Tumors or hyperplasia of adrenal cortex (Cushing's syndrome)
   - Basophilic tumors of the pituitary gland
   - Menopausal
3. *Cardiac and vascular disorders*
   - Hyperthyroidism
   - Aortic regurgitation
   - Congenital lesions, as arteriovenous fistulas
   - Coarctation of the aorta
   - Arteriosclerosis of large-vessel type
4. *So-called neurogenic hypertension*
   - Anxiety states, acute or chronic
   - Psychogenic stimuli, as fear, anxiety and rage
   - Diseases of the brain itself, as tumors of the brain
   - Disturbances of the vasomotor centers of the brain
   - Disturbance of right and left aortic carotid sinus nerves
5. *Essential hypertension*
   - Benign or the presclerotic and the early arteriosclerotic stages (corresponding to Wagener and Keith classes I and II)
   - Premalignant or transitional stage between benign and malignant (grade III)
   - Malignant hypertension (grade IV)

### *Essential Hypertension*

The nature of essential hypertension is a problem about which there is no unanimity of opinion. Its cause is unknown. It is interesting to note, though, that at present the leaders in this field continue to discuss the relationship of the kidney, the arterioles and the hypertension.

Essential hypertension was the term first popularized and used by Frank[6] to include those cases of chronic high blood pressure which were neither clinically nor anatomically associated with inflammatory diseases of the kidneys or the urinary tract. The definition is defective in that it is one by exclusion and admits lack of knowledge of the cause.

Volhard and Fahr[7] classified essential hypertension into the benign and malignant forms. The two differ only in degree of severity, speed of progress and ultimate outcome. In 1939 Wagener and Keith[8] further classified essential hypertension into various groups using the ophthalmoscopic features, since the retinal arterioles are an index of the condition of the arterioles elsewhere in the body.

Smithwick[9] has also classified hypertension into four groups, according to the changes in the cardiovascular system. An attempt was made to take the response to sedation, the resting diastolic blood pressure level and the age of the patient into consideration as well. This classification and that of Wagener and Keith have been used as a basis for determining the prognosis and treatment of many patients with essential hypertension.

### *Management*

*Medical*—The rational method of treatment would be to remove the cause, but, since the cause is not known, treatment must be limited to palliative measures. In the management of hypertension, the assessment of the blood pressure becomes of some importance, since it is a guide in determining the amount and kind of treatment.

There is a tendency to view the blood pressure separately and to consider all high blood pressure as equally significant. The natural history of hypertension contradicts this view. As reported previously, a blood pressure of 160/100 may be compatible with good health, vigorous life and old age.[10]

The difficulty in the treatment of hypertension is that the disease may take a variable course naturally, and therefore the results are difficult to evaluate. What constitutes hypertension has been a topic of discussion for many years by Master and Jaffe[11] who believe that our modern definition is entirely too rigid and that as a result many false diagnoses are made. They set up new criteria as follows: A systolic pressure of 150 to 160 may be normal in a man or woman 40 to 50 years old, and a systolic pressure of 170 may be normal in a man over 60, and 175 in women over 60. A diastolic pressure of 96 may be normal in persons of 45 to 50 years and a diastolic pressure of 100 may be normal over the age of 50. In fact, even higher blood pressures than these may also be normal—i.e., those between these upper limits of normal and the definitely hypertensive levels for each age and sex. Further, treatment becomes difficult to evaluate in these patients, for benefits often are falsely attributed to the agent or drug used. The old *post hoc, ergo propter hoc* error in therapeutics is often the result.

*General measures*—To determine which patients are destined for early trouble and which ones may escape complications is difficult, but it is always safe advice to attempt to control excessive hypertension when it exists. General measures and symptomatic treatment are sufficient in many instances to control moderately high blood pressure. This requires an inquiry into the patient's mode of living, daily habits and diet. These measures may prove beneficial, especially if performed in conjunction with a careful, sympathetic understanding of the patient's troubles. Many times a blood pressure falls to normal after some emotional factor is removed.

Attention to a patient's habits may be of considerable importance in many instances. At times more rest, more recreation and less work may have a twofold beneficial effect. They may not only lower blood pressure but simultaneously may lessen the heavy load on the heart. Changing one's job is hardly ever

advisable if the emotional strain associated with such changes may offset any beneficial result acquired therefrom.

Much has been said on the use of tobacco, but we believe that patients should stop smoking immediately, for they will usually begin to feel better and progress more satisfactorily. As for the use of alcohol, there is a greater diversity of opinion. Patients accustomed to use of alcohol in moderation may continue its use. Coffee and tea, even though they are mild stimulants, are not contraindicated because their judicious use by the patient may have a relaxing effect.

*Diet*—For over 50 years dietary regulation has been heavily relied on in the treatment of essential hypertension. Restriction of the total intake of calories, the deprivation of salt, and the reduction of fat and cholesterol have been the chief features. It is fairly well accepted that reduction of food resulting in reduction of weight leads often to a lowering of high blood pressure.

Use of the salt-restricted diet as a therapeutic measure came into popularity before it was known to have anything to do with high blood pressure. It was thought originally that chloride retention was the basic factor in cardiac and renal edema.[12] However, Blum et al.,[13] Magnus-Levy[14] and Vogel[15] have stated that retention of the sodium ion and not the chloride ion is the chief factor in the pathogenesis of edema. Following the basic work of chloride retention as a factor in the pathogenesis of edema, the groundwork was laid for the application of salt deprivation in the treatment of hypertension. In 1920 Allen[16] brought the therapeutic possibilities of rigid salt restriction in the treatment of hypertension to the attention of the American medical profession. More recently Martini and Kaiser[17] treated patients with high blood pressure with salt restriction, and the blood pressure decreased. They then added to the salt-free diet a chloride-containing substitute (containing 40.4 per cent chloride), up to 12 gm. a day. This was not followed by elevation of blood pressure. They then added, instead of the chloride-containing substitute, a sodium one (containing 43.2 per cent sodium), up to 12 gm. daily. Again the blood pressure remained at a low level. After that, they gave 12 gm. of sodium chloride and the blood pressure rose significantly. In their opinion, it is obvious that neither the sodium itself nor the chloride itself is able to increase blood pressure but that the combination of the two will do it. The active agent must be the sodium chloride molecule.

Kempner[18] believes that the rice diet, which is salt-poor, protein-poor and fat-poor, is of value in treatment of hypertension. Results recently published[19] led him to believe that intensive dietary treatment should be started as early as possible and continued until all signs of vascular disease have disappeared. The improvement in 177 patients with advanced neuroretinopathy, whose survival time would be low ordinarily, was impressive in this series, at least in those who did not have significant renal impairment and did not lose significant quantities of sodium in the urine. Watkin et al.,[20] in a two year investigation of the Kempner rice regimen in 50 patients with advanced essential hypertension, found that their results corroborated those of Kempner but that the regimen in its present form imposes such hardship on the patient and so much difficulty in control as to make it virtually impracticable for general use.

Goldring[21] believes there is no evidence that the low protein content of the so-called rice diet in any way influences the level of the blood pressure. Goldring does not think there is any point in restricting the diet for the purpose of reducing the blood pressure itself.

From reviewing the opinions of others and our own experience, it seems that salt restriction may be helpful in some cases, harmful in a few and certainly not beneficial in all cases of hypertension. We have usually restricted sodium in premalignant and malignant hypertensive patients to from 250 to 500 mg. In benign hypertensives, an average of 1600 mg. of sodium is given, but we have been unable to determine a definite therapeutic result.

Use of a low fat diet theoretically has some interest in the prevention of arteriosclerosis. However, it is doubtful that it contributes basically to the reduction of blood pressure.

Nevertheless, in constructing a low calorie diet, restriction of fats is desirable.

Gold[22] believes that dehydration as a measure in treating hypertension is worthy of more careful consideration. His procedure is to put the patient at complete bed rest and restrict him to 1½ gm. of salt and six glasses of water daily. In addition, 2 cc. of MERCUHYDRIN® is given intramuscularly daily. Within two weeks, he says, a radical change is evident. As time goes on, the treatment is adjusted to individual requirements.

*Drugs*—The pharmacologic treatment of hypertension was opposed for many years because it was felt that the hypertension was a compensatory mechanism of the body. It has since been shown that reduction of blood pressure in the hypertensive patient is not harmful except in a few patients who have rather marked arteriosclerotic involvement of the blood vessels of the brain, heart and kidneys.

Many drugs have been enthusiastically recommended for the treatment of hypertension, but after a short time were found lacking and passed into disuse. The nitrites and thiocyanate were popularly used as hypotensive agents, but due to their many side effects and their difficulty of control they have been almost abandoned.

In recent years, drugs with entirely different actions have come into use. No one drug discovered so far is ideal. All fail to be completely effective in every case. Many have serious side effects, and none corrects the fundamental defect causing hypertension. However, these newer preparations do lower the blood pressure effectively and, in many cases, delay or prevent the serious complications of hypertension. While there is no perfect drug, these preparations represent a definite advance in the treatment of high blood pressure, and the results of medical treatment now are better than formerly. This advance, however, must be considered only a step toward the goal of finding the ideal preparation which would be one that corrects the hypertension by eliminating the cause.

The introduction of these newer preparations has placed an additional burden on the attending physician as well as on the patient. Contrary to the ideas of some, the treatment of hypertension has become more complicated and more time-consuming, especially because of the serious side effects associated with drugs. The full cooperation of the patient is important, and the physician must devote considerable time explaining the patient's blood pressure to him and directing the precise use of the newer methods. If the patient does not wish to fulfill his obligation and carry out instructions with precision, it is better not to start the treatment at all. Likewise, if the doctor does not wish to devote an adequate amount of time for full discussion and analysis, then it is better that he, too, does not attempt treatment.

The physician must decide if the drugs are necessary at all, as high blood pressure may drop to normal with little or no specific treatment. Furthermore, he must consider the risk involved in using the drugs and decide if it is justifiable. It is best to discuss these points with the patient.

It is essential to emphasize again that not all patients with hypertension need be treated with the more powerful modern hypotensive agents, as some are not benefited and some are made worse. Frequently a reduction of weight (if the patient is obese), an adjustment of occupation, changes of habit (if necessary), and perhaps a minimum of drug treatment may be all that is necessary. But there are those patients with essential hypertension of grades III and IV who always require more rigid treatment.

Our experience with drug therapy of high blood pressure is summarized in the following 59 cases selected from the hypertensive clinic of the Milwaukee County Dispensary and hypertensive service of the Milwaukee County Hospital. Many more patients with high blood pressure have been studied and treated with drugs but because of poor cooperation on the part of the patient, they have not been selected for this report. All patients in this series have been closely observed for from four months to 15 years, both on an outpatient and on an inpatient basis.

Most patients in the selected group are living. The largest mortality has been in the ma-

TABLE 2

HYPOTENSIVE DRUGS FOR ORAL THERAPY*

| DRUG | FORM AND DOSAGE | ACTIONS | UNDESIRABLE SIDE EFFECTS |
|---|---|---|---|
| Rauwolfia serpentina | 1. Crude root powder; dose, 100 mg. one to four times daily<br>2. Alseroxylon fraction; dose, 2 mg. one to four times daily<br>3. Reserpine, pure alkaloid; dose, 0.1 to 0.25 mg. one to four times daily | Sedative, bradycardic, mild hypotensive, central (?) adrenergic-blocking, increase of bowel motility | Nasal stuffiness, gain in weight, depression, dreams |
| Hydralazine (synthetic of hydrazine) | Hydralazine hydrochloride; dose, 10 to 150 mg. four times daily | Central and peripheral adrenergic-blocking, general and renal vasodilator | Cardiac stimulant, causes tachycardia and palpitation, and, in coronary disease, angina. Causes headache; may cause fever, arthritis, rash, "collagen disease" and mental changes |
| Veratrum | 1. Crude root powder or suspension; dose, according to animal assay<br>2. Protoveratrine (pure alkaloid); dose, 0.25 to 0.75 mg. four times daily<br>3. Various alkaloids and mixtures of alkaloids; dose, according to animal assay | Central neurogenic vasodilator and vagal bradycardic agent | Nausea and vomiting, arrhythmias, collapse |
| Hexamethonium | Chloride; dose, 31.25 to 750 mg. four times daily | Total autonomic ganglionic blockade, hypotension (especially orthostatic) | Obstipation, postural hypotension, weakness, lack of visual accommodation, bladder atony, dry mouth, impotence, vasomotor collapse, depression of renal function |
| Ansolysen | Ansolysen tartrate tablets; dose, 20 to 100 mg. four times daily | Another autonomic blocker | Same as with hexamethonium |

*Modified after Wilkins.[21]

lignant hypertensive group, in which 90 per cent have died. In general, however, these patients came to us fairly late in the course of their disease, and succumbed in spite of intensive therapy. (We feel their inclusion is justified since some of them had known of their disease for only a few months prior to death. Malignant hypertensive patients first seen in the terminal state are not included.)

As could best be determined, the patients in this series all have essential hypertension. The diagnosis was established by the usual history and physical examination, and routinely the following work-up: hemogram, electrolyte panel, chest film, intravenous pyelograms, occasional retrograde pyelograms, electrocardiograms, REGITINE® and/or benzodioxane and renal function studies (Volhard's test, Addis count, P.S.P., urea clearance, 24 hour quantitative protein, and in some cases mannitol and

TABLE 3

BLOOD PRESSURE RESPONSES TO USE OF DRUGS*

| | ANSOLYSEN | APRESOLINE | HEXAMETHONIUM | RAUWOLFIA | VERATRUM |
|---|---|---|---|---|---|
| Patients treated | 10 | 44 | 8 | 16 | 17 |
| Diastolic decrease 20 mm. | 8† | 17 | 6† | 2 | 0 |
| Average effective daily dose (mg.) | 300 | 530 | 1,525 | 300 | 18‡ |
| Range of dosage | 120-620 | 150-800 | 750-2500 | 150-400 | 12-24 |
| Side effects | 10 | 30 | 8 | 6 | 10 |
| Discontinued drug because of side effects | 1 | 12 | 2 | 2 | 4 |

*Combination therapy with Rauwolfia.

†Sustained reduction 20 mm. Hg diastolic.

‡No response.

P.A.H. clearances). If one of the rare causes of high blood pressure was suspected, special studies were done to rule out this cause. Only in a few cases maintained on ganglionic-blocking agents have we relied on home blood pressure readings. Blood pressure recordings in this series are basically monthly averages of pressures obtained in the outpatient department and weekly averages of daily hospital pressures.

The patients' ages ranged from 28 to 76 years. Twenty-two were men and 37 were women; 31 were Caucasians and 28 were Negroes. Of the hypertensive cases included in this series, 44 were benign, 5 premalignant and 10 malignant.

The hypotensive drugs used in this study were the following: Rauwolfia, hydralazine (APRESOLINE®), Veratrum (VERILOID®), hexamethonium and pentapyrrolidinium (ANSOLYSEN®). As has been reported by others,[23] the mild hypertensive patients (grades I and II) were treated with mild hypotensive therapy; correspondingly, the severe hypertensive patients (grades III and IV) were treated more intensively with the more potent agents in combination with the milder drugs to allay side reactions.

Table 2 is our revision of one by Wilkins[24] and is a modification of our own procedure.

Grimson[25] has pointed out that there are wide differences of opinion concerning the choice of drugs and arrangements of dose schedules for hypertension. Some authorities advise observation and reassurance without medication; others advise sedation by barbiturates or use of extensively advertised "mild hypotensive" drugs such as hydralazine or Rauwolfia.

It has been our plan to hospitalize patients and begin all except severe cases on Rauwolfia in doses ranging from 50 to 100 mg. three times a day for three to four weeks. At the end of this time, if a change in blood pressure levels did not occur, therapy with either Veratrum (Veriloid) beginning with 3 mg. daily and increased in 3 mg. increments every four to seven days, or Apresoline starting with 50 mg. daily and increased by 50 mg. increments every two to three days was instituted. Dosages were progressively increased until either side effects forced discontinuation of therapy or lowering of blood pressure resulted. Maximum dosage (Veriloid 24 mg. and Apresoline 800 mg.) is continued for at least three months if the patient can tolerate it.

We reserved hexamethonium and Ansolysen for severe benign, premalignant or malignant hypertension when other agents failed. Frequently patients are started on the parenteral form of the blocking agents and then shifted to oral therapy, the dosage in either case being adjusted according to response of the standing blood pressure. In practically all cases, combination therapy was used—that is, the agent plus a Rauwolfia preparation. Table 3 shows the blood pressure response in our series.

Rauwolfia was found to be effective in the mild grade of hypertension only, but was a basic treatment on which the potent agents

TABLE 4

UNDESIRABLE SIDE EFFECTS OF HYPOTENSIVE DRUGS

| SIDE EFFECT | ANSOLYSEN (10 patients) | APRESOLINE (44 patients) | HEXAMETHONIUM (8 patients) | RAUWOLFIA (16 patients) | VERATRUM (17 patients) |
|---|---|---|---|---|---|
| Headache | | 19 | | | 1 |
| Malaise | | 11 | | 2 | |
| Postural hypotension | 10 | | 8 | | |
| Constipation | 10 | | 8 | | |
| Nausea | | 8 | | | 9 |
| Palpitation | | 7 | | | |
| Apprehension | | 5 | | | |
| Arthralgia | | 4 | | | |
| Nasal stuffiness | | | | 4 | |
| Flushing | | 3 | | | |
| Blurring of vision | 2 | | 2 | | |
| Edema | | 2 | | | |
| Chest pain | | 2 | | | |
| Vertigo | | 2 | | | |
| Dryness of mouth | | | 2 | | |
| Urinary retention | 1 | | 1 | | |
| Dyspnea | | 1 | | | |
| Nightmares | | | | 1 | |
| Agranulocytosis | | 1 | | | |

were built. The diastolic blood pressure was reduced significantly in only 2 out of the 16 patients (12 per cent). Little difference was encountered whether the whole root was used or the purified alkaloids. Side effects were encountered in 6 of 16 patients (37 per cent), but it was necessary to discontinue therapy in only two of the cases because of side effects, the chief one being nasal stuffiness. Many patients experienced a state of well-being, probably due to the tranquilizing effect of Rauwolfia. As a result of this, they noticed an increased appetite, and it was necessary to encourage them to follow their diets closely. The bradycardic action of Rauwolfia may be of significance if the patient is digitalized, especially with purified cardiac glycosides. If the pulse is slow, it may be difficult to determine if this is due to the action of Rauwolfia or the result of overdigitalization. The use of digitalis leaf may simplify management in that symptoms resulting from overdigitalization, such as nausea and vomiting, will give the physician a clue as to the bradycardia.

Apresoline was found to be effective in reducing the blood pressure in 17 of 44 patients (38 per cent). It appeared to be equally effective in both benign and malignant hypertension. The incidence of side effects was high; 29 of these patients had various complaints, forcing discontinuation of therapy in 12 cases (27 per cent). The side effect of Apresoline is a histaminelike reaction. Nineteen of the patients complained of headache and some of these obtained relief by using an antihistaminic agent. In those who did not respond to this, the headache usually would diminish if the therapy was continued in a low dosage

TABLE 5

REVERSAL OF THE COURSE OF MALIGNANT HYPERTENSION BY USE OF DRUGS

R. L., 46 year old white man

| DATE | BLOOD PRESSURE | DRUG AND DOSAGE | COMMENT |
|---|---|---|---|
| 5/27/53 | 210/140 | BISTRIUM®, about 85 mg. four times a day for 11 days | Subarachnoid hemorrhage nine days before; fundi, 4 |
| 6/8/53 | 180/125 | Bistrium, 75 mg.; Apresoline, 100 mg. by mouth | Frequent hypotensive episodes; disoriented; fundi, 4; hematuria, 6/11 |
| 6/24/53 | 138/98 | Apresoline, 400 mg. orally | Papilledema, trace; nonprotein nitrogen, 42. Discharged 7/1 |
| 9/21/53 | 120/90 | Apresoline, 800 mg. by mouth; RAUDIXIN®, 150 mg. | Rx one year; asymptomatic; fundi, 2; working |
| 4/25/55 | 150/90 | Raudixin, 150 mg. | Asymptomatic; fundi, 2; patient working regularly |

range over a two week period. Almost all patients noticed some malaise when dosage was increased over 300 mg. daily, but it was a prominent complaint in 11. No effective means of combating this was found. Tachycardia, which almost always occurred, could be diminished by the use of Rauwolfia. Our experience in cases other than the ones reported here indicates that Apresoline may also produce mental disturbances, even mania. We did not observe any cases of the lupus syndrome reported by Dustan[26] even though high dosage was continued over several months. However, arthralgia developed in four cases, requiring discontinuation of therapy. One patient with benign hypertension who was on a moderate dosage for a short period developed agranulocytosis and died.

Veratrum proved impractical in this particular series in that the toxic range was close to the therapeutic one. Of the 17 patients observed, none had a significant diastolic reduction. It was noted that an initial hypotensive effect was obtained, but this could not be sustained over a long period. Nausea and vomiting occurred in 9 of the 17 patients, forcing discontinuation of therapy in four cases. Chlorpromazine was tried in an effort to reduce the incidence of nausea and vomiting but was not found to be effective except in one patient. The addition of Rauwolfia to the Veriloid regimen did not significantly alter the incidence of side effects.

Hexamethonium and Ansolysen were found to be effective hypotensive agents. A reduction of blood pressure was obtained in all 18 patients observed, but a sustained reduction was maintained in 14. The hypotensive effects of hexamethonium and Ansolysen appear to be similar except for the differences in size of dosage required to produce equivalent blood pressure reduction. Side effects result from both sympathetic and parasympathetic ganglion-blocking action, the chief side effect being postural hypotension, which in some cases was severe enough to cause collapse. Constipation was also of importance in these patients and was best handled by the use of PROSTIGMIN® daily. Pilocarpine orally was found to reduce the incidence of blurring of vision, but in itself could produce diarrhea.

Table 4 shows the composite results of side effects of antihypertensive therapy.

While drugs have a prominent place in treating hypertension, they do not answer the problem completely. Tables 5 and 6 show their effects in two cases. Blood pressure was reduced in both instances, and yet one of the patients died (table 6). Table 5 is self-explanatory. The blood pressure was controlled and the patient became asymptomatic. Table 6 shows that reduction of blood pressure is not the only problem of hypertension. Over a period of several months, although the blood pressure was practically controlled, the associated arteriolar changes were not modified

TABLE 6

EFFECT OF DRUGS IN MALIGNANT HYPERTENSION

L. A., 46 year old Negro man

| DATE | BLOOD PRESSURE | DRUG AND DOSAGE | COMMENT |
|---|---|---|---|
| 2/8/55 | 250/150 | | Headache, nausea, vomiting. Hematuria; nonprotein nitrogen, 56; $H_1P_3$ |
| 2/9/55 | 50/10 | Ansolysen, 3 mg. subcutaneously | Shock |
| 3/4/55 | 145/105 | Ansolysen, 220 mg. orally; Raudixin, 200 mg. | Nonprotein nitrogen, 41; discharged asymptomatic; no hemorrhages. Papilledema gone 4/20/55 |
| 5/17/55* | 250/150 | Apresoline, 120 mg. intramuscularly; Ansolysen, 320 mg. by mouth | Fundi, $H_2P_1$. Nonprotein nitrogen, 85 |
| 6/3/55 | 110/70 | Ansolysen, 160 mg. by mouth; Raudixin, 300 mg. | Asymptomatic; nonprotein nitrogen, 84. Discharged |
| 7/19/55* | 235/140 | Ansolysen, 340 mg. orally | $H_0P_0$; nonprotein nitrogen, 107; marked postural hypotension; urinary retention |
| 7/26/55 | 250/160 | Apresoline, 80 mg. intramuscularly | Comatose; left hemiparesis |
| 7/28/55 | 240/155 | Apresoline, 120 mg. intramuscularly | Patient died. Postmortem examination: malignant nephrosclerosis and right cerebral hemorrhage |

*Readmitted symptomatic; patient could not work and take Ansolysen due to hypotension.

to any great degree, as shown by the fact that the patient died of a cerebrovascular accident months later. While some authors feel that the arteriolonecrosis seen in malignant hypertension is stopped by the use of drugs, this is not always the case. Occasionally a patient with all the features of the disease will suddenly, without known cause and independent of the treatment, pass into a state of remission during which the blood pressure falls practically to normal and the signs and symptoms disappear.[27]

Stress is another factor one must take into consideration in managing the hypertensive patient. We feel that bed rest and sedation will reduce blood pressure in many instances, but unfortunately this factor has not been completely evaluated at this time in our series of patients. In a few selected cases we have noticed marked changes in blood pressure when the patient is hospitalized and not given specific drug therapy.

*Surgical*—Obviously, difficulty arises in determining which patients will be benefited by radical operation and which will live satisfactorily without it. When the hypertensive patient is given the alternative of having the operation or facing early death from heart-failure, stroke or some other dire complication, the decision becomes obvious.

Sympathectomy—Although in some cases sympathectomy has been successful, there are several disadvantages: (1) Not all patients are suitable for the operative procedure. The young or middle-aged are the best candidates (those between 30 and 40 or 45 years with a relatively high diastolic (120 to 140) and a relatively low pulse pressure (50 to 70 mm.) reacting well in blood pressure levels to change in posture, to cold, etc.). (2) This operation is always a major one which demands a long convalescent period. (3) It is impossible beforehand, despite the elaborate measures for determining suitable patients, to say which ones will be benefited. In determining the outlook for individual patients, one must consider such chief factors as the preoperative level of the diastolic pressure, the condition of the brain, the eyegrounds, heart and kidneys, and response to sedation. The duration of hypertension is always important, too, but it is rarely possible to obtain exact information

regarding this. Kirkendall and Culbertson[28] state that their single absolute contraindication to sympathectomy is progressive renal insufficiency.

At present there is no unanimity of opinion regarding the advisability of sympathectomy for hypertension. Many clinicians believe it is a measure too drastic and extensive for most patients with high blood pressure, and since the advent of the modern drugs the indications have further diminished. However, Huntington and Evans[29] point out that sympathectomy may prove to be the treatment of choice in certain young patients with grades III and IV hypertension so they may not need to be dependent on drugs for the rest of their lives. Also, the additional weapon of drug therapy could be used if the hypertension recurred.

Considering the fact that the majority of hypertensive persons live useful lives without discomfort for many years, the group which should be subjected to surgery becomes quite narrow. For the hypertensive patient under the age of 50 years with a progressively increasing hypertensive picture of grade III or IV and who has the prodromata of some serious complication, this operation should be considered. But for the individual with hypertension who does not have such chief symptoms as headache, impending heart-failure or stroke it is probably best to treat him conservatively and by medical measures.

Adrenalectomy—Severe hypertension has also been controlled by removal of the adrenal glands with or without sympathectomy.[30-32] While there have been some good reports from initial investigation, it is too early to evaluate the ultimate results.

Pickering[4] contends that subtotal or total adrenalectomy now has little or no place in the treatment of hypertension. Not only is life without adrenals very precarious even with our present array of substitution products, but the results with the methonium salts, with or without hydralazine and Rauwolfia, are so promising as to suggest effort should be canalized in this direction. Radical measures of treating high blood pressure should be reserved for those patients in whom adequate medical care has failed.

### *Comment*

The use of the newer hypotensive drugs, in our opinion, has been too promiscuous in the modern management of hypertension. This does not imply that these potent pharmacologic agents should not be used or that we belong to the school of therapeutic nihilism. Rather, we recommend caution in the use of these drugs after attention has been given to psychosomatic factors and diet control. Since the course of hypertension may be reversible, even though it is a slowly progressive disease, early treatment is recommended in order to prevent or delay cerebral, cardiac or renal damage which often deprives the patient of many years of useful, productive life.

In common with many authors,[24,33-40] we have observed gratifying blood pressure reduction and favorable results by judicious antihypertensive therapy. Drugs were introduced by beginning with the milder agents and progressing to the more potent ones.

Rauwolfia, or one of its derivatives, is the mildest of the hypotensive agents. Use of this drug alone is often accompanied by unpleasant side effects but in combination with other agents it has proved effective in our experience. Doyle, McQueen and Smirk[34] found it reduced blood pressure in only 10 of 40 patients and that the administration of Veratrum alkaloids in addition to reserpine did not produce any further hypotensive effect. However, they report the administration of reserpine in combination with pentapyrrolidinium led to an improvement in the hypotensive action. Rauwolfia was regarded as a useful hypotensive remedy for mild hypertension by Vakil[41] but the severer forms were best treated with combined therapy. In 61 per cent of cases on combined therapy of the powdered root and Veratrum viride there was subjective improvement. Sixty-seven per cent of patients on the powdered root and hexamethonium were also improved.

Apresoline has been, in our experience, an equally effective agent in both benign and malignant hypertension. When used alone, side effects were more prominent. Administering it in combination with reserpine, Hughes,

Dennis and Moyer[38] found 87 per cent of 15 patients obtained a significant drop in blood pressure and 33 per cent became normotensive. With a combination of hexamethonium and reserpine the same authors reported 84 per cent of 32 patients were responsive to combined therapy and 47 per cent became normotensive. When reserpine in combination with hexamethonium was used, the dosage requirement of hexamethonium was reduced significantly, and the blood pressure response was more stable in comparison with the use of hexamethonium alone.

Corcoran et al.[33] have used hydralazine and hexamethonium alone and in combination. Sustained relief and decreased mortality followed the use of hydralazine in about half the patients treated. Experience with hexamethonium alone shows that it gave temporary relief in 16 of 17 patients with malignant hypertension; the duration of relief was limited by tolerance to its depressor effect on supine diastolic pressure. Benefit was not determined by persistence of orthostatic hypotension. Our own experience paralleled that of Corcoran and associates.[33]

In our series we found Veratrum an impractical agent. The observations of Fishberg[42] support these findings, for he states that he has known few instances of essential hypertension in which Veratrum preparations have seemed to help the patient. Saphire[43] found that Veriloid demonstrated considerable ability to lower blood pressure. It appeared to be equally effective in malignant and nonmalignant hypertension, and in hypertension of renal origin as well as essential hypertension. Veriloid, however, was less effective with increasing duration of hypertension; 90 per cent of patients had subjective improvement, and in 60 per cent improvement was considerable.

The hypotensive actions of hexamethonium and pentapyrrolidinium, according to Smirk,[35] appear to be similar except for differences in the size of doses required. In combination with Rauwolfia, these agents are useful hypotensive agents. Generally speaking, this has been our experience.

Just which combination of therapy should be used is a matter of personal preference. Rauwolfia has decreased the side effects of all other agents when used in combination with any of them. Probably the best guide is to use the milder agents in combination for treating hypertension of grades I and II; the more potent agents in combination with Rauwolfia are most effective in grades III and IV.

The prescribed dosage of these drugs is another problem. We believe it is a waste of the patient's money and the physician's time not to give drugs in their full therapeutic dosage. If drugs are to be used, they should be given to obtain a full therapeutic effect—that is, until one gets a blood pressure reduction. If this does not occur within a reasonable period, drug therapy should be discontinued.

For the physician who has had little experience with the antihypertensive drugs, Smirk[41] recommends that dosages of the agents be adjusted by reported hypotension symptoms rather than on the basis of blood pressure readings taken by the physician after the preliminary period of dosage determination is passed. Often, office blood pressure readings may be in error due to the psychogenic elevation on seeing the physician. We believe, too, that home blood pressure readings may be subject to the same error. The patient is made acutely aware of the numerical factor of his disease. We have therefore abandoned use of the procedure.

As pointed out by Schroeder,[45] the use of these antihypertensive drugs, as with all potent drugs, involves a calculated risk. The risk, however, is relatively small in relation to the risk inherent in the disease. We believe, too, that the present set of antihypertensive drugs in use may be considered, to a large extent, precursors of a more practical set of drugs of the future.

Some of the auxiliary methods in treatment of hypertension, especially of the benign essential type, have been neglected in favor of the potent antihypertensive drugs. This we consider to be a therapeutic error, as we believe in some instances that simple measures are all that are necessary to control the blood pressure. At times, the use of agents which involve risk may well be deferred until a later date when hypertension is uncontrollable. Hy-

pertension is probably a disorder in which many factors participate. A therapeutic attack on one angle of the disease without considering the patient as a whole is indefensible.

### *Summary*


1. In evaluating the methods of treatment of hypertension, the use of drugs and their actions have been overemphasized to the neglect of other methods of treatment, such as the role of the diet and the psychosomatic factors—e.g., the patient's mode of living and habits. These points are given attention in this paper, along with the authors' experience with the newer drugs. Also considered is the surgical treatment of hypertension by means of sympathectomy and adrenalectomy.

2. The new drugs alter one factor of the disorder, namely, high blood pressure itself, and generally fail, as far as we know, to modify some essential conditions which are a part of the disease. This relationship of the high blood pressure to the metabolic, humoral and vascular changes associated with it is one of the disputed questions of the day, and a short discussion is given.

3. A classification of hypertension is presented, for it is believed important in evaluating the patient with high blood pressure. It is emphasized that it is essential hypertension in which the hypotensive drugs are most applicable.

4. To determine which patients are destined for early trouble and which ones may escape complications is difficult, but it is always safe advice to attempt to control excessive hypertension whenever it exists. General measures and symptomatic treatment are sufficient in many instances to control moderately high blood pressure. Attention to the patient's habits, more rest, more recreation and less work may have beneficial effect. These are discussed.

5. Reduction of calories resulting in reduction of weight often leads to a lowering of high blood pressure. Restriction of total intake of calories, deprivation of salt and reduction of fat and cholesterol have been the chief factors in dietary regulation.

6. Drugs, when used, should be introduced beginning with the milder agents, progressing to the more potent ones. In mild hypertension (grades I and II), mild hypotensive drugs should be used; in severe grades of hypertension (grades III and IV), more intense and potent agents in combination with the milder drugs to allay side reactions are used.

7. Our experience with 59 selected patients followed for periods of from four months to 15 years both as outpatients and as inpatients is reviewed. The hypotensive drugs used in this study were Rauwolfia, hydralazine, Veratrum, hexamethonium and pentapyrrolidinium. Our results parallel those of other authors in that we observed gratifying blood pressure reduction with judicious drug use. However, we believe that while drugs definitely have a place in treating hypertension, they do not answer the problem completely. Other factors such as stress also must be considered.

8. Since the advent of the newer drugs, indications for drastic surgical measures such as sympathectomy have further diminished. Considering the fact that the majority of hypertensive persons live useful lives without discomfort for many years, the group which should be subjected to surgery becomes quite narrow. Adrenalectomy also has been reported as of aid in treating severe hypertension, but it is too early to evaluate ultimate results.


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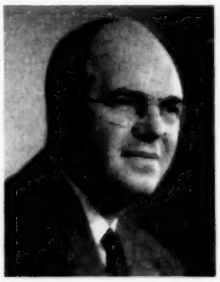
# The Prevention of Retrolental Fibroplasia

## THE SCHNEIDER FOUNDATION EYE PRESENTATION

JOHN C. LOCKE*

*McGill University, Montreal*

Loss of sight from retrolental fibroplasia represents blindness in its most tragic form. Unlike persons blinded later in life, children with this disease have never seen the world about them, and their physical, mental and emotional development must take place under this handicap to more normal development.



JOHN C. LOCKE

Fortunately, in the past year or two the cause of and the means of preventing this commonest cause of blindness in childhood have been discovered and proved. It is now important that our newly acquired knowledge be disseminated as quickly as possible so that unnecessary cases will no longer occur.

Most physicians are aware that retrolental fibroplasia is caused by excessive administration of oxygen in the early days of a premature baby's life, but certain practical points in preventing the disease require emphasis. This is particularly true in view of the fact that modern incubators with improved facilities for providing high oxygen concentrations are becoming available to more and more hospitals; more widespread opportunities for producing the disease are therefore accompanying advances in our knowledge of how to prevent it.

Two schools of thought exist regarding the degree of prevention possible. One believes that after all oxygen toxicity has been eliminated there still will be an "irreducible minimum" of retrolental fibroplasia due to other causes, at present unexplained. This opinion is based on what may prove a fallacy—namely, that the disease can occur in full-term infants or in premature infants who have never received oxygen. Since the end stage of retro-

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lental fibroplasia is often differentiated with difficulty from other causes of a white pupillary reflex (leukocoria), the diagnosis is not justified unless the condition has been followed from its inception through characteristic clinical stages.* While the literature contains reports of presumed cases, it is difficult to find any which satisfy the necessary criteria for a proved diagnosis. On the other hand, a recent survey in the United Kingdom[1] of the incidence of RLF among 344 babies weighing 4 lb. or less at birth showed that none of the babies who had not had oxygen developed the disease. The incidence of the disease rose steeply with increasing length of oxygen treatment. A controlled cooperative study in the United States[2] involving 18 hospitals and 391 infants weighing 3 lb. 5 oz. or less at birth gave similar results. Finally, in my series of more than 500 small premature babies who were examined ophthalmoscopically at weekly intervals from birth, not even the earliest signs of retrolental fibroplasia appeared in any baby who had not received oxygen for at least three days.

The second school of thought, the one that my experience leads me to support, holds that *complete prevention* of the disease through proper oxygen control is an entirely plausible goal. At the Maternity Pavilion of the Royal Victoria Hospital, during the past 15 months, Dr. Philip Banister and I have followed 72 consecutive babies weighing 4 lb. or less at birth, with no evidence of even the mildest manifestations of the disease. This number admittedly is smaller than desired, and we are continuing our study, but by comparing these results with earlier experience[3,4] it has become apparent that certain important principles in regard to the administration of oxygen must be followed meticulously if babies are to survive and retrolental fibroplasia is to be completely prevented. The following general recommendations are the result of our experience as well as that of others:

1. Oxygen should never be given as a routine measure; it should be administered only when there are clinical indications for its use, and then in the lowest concentrations and for the shortest periods consistent with the patients' needs. The initial concentration should not be higher than 40 per cent and this should be reduced as quickly as possible. In many cases lower concentrations are sufficient. For babies needing oxygen over a long period, Banister has shown that concentrations as low as 22 to 26 per cent often are effective. In other cases oxygen need only be given intermittently for short periods. To control and maintain lower concentrations effectively, we recommend a more sensitive flowmeter such as the Rotameter,* which allows changes in flow rate of tenths of a liter.

2. Every nursery with facilities for giving oxygen to premature babies *must have an oxygen analyzer*. Oxygen should then be ordered *by concentration and not by liter flow*, since there is no adequate correlation between the oxygen concentration in the incubator and the flowmeter setting. Settings as low as 1 or 2 l. per minute occasionally may give concentrations of oxygen as high as 50 or 60 per cent.

3. Oxygen concentrations in the incubator should be *measured and charted at regular intervals*, not less than once every two hours, day and night. (Each of these measurements can be taken in a matter of seconds.)

4. Readings taken within 30 minutes of changing the flow rate or opening the incubator lid or sleeves may be inaccurate because there will not have been time for the oxygen concentration to become stabilized. The readings should therefore be repeated after the half-hour has passed.

5. Since the baby's oxygen needs vary during the day, the control of the oxygen must be under constant surveillance. The nursing staff must have the necessary training and authority to reduce the oxygen when it is apparent that the baby can get along with less, or to increase it if necessary.

6. The chief indication for oxygen therapy is cyanosis. Periodic or irregular respiration in the absence of cyanosis no longer is considered an indication for administration of oxygen.

*The clinical manifestations and histopathology of retrolental fibroplasia were briefly illustrated by lantern slides.

*Rotameter Manufacturing Co. Ltd., 602 Purley Way, Croydon, England. Canadian agent: J. L. McDougall, 1545 McGregor St., Montreal.

7. Some incubators designed before the dangers of oxygen toxicity were known have an attachment for providing a supersaturated environment which is dependent on an inflow of oxygen. If supersaturation is desired in cases not needing oxygen, a compressed-air pump rather than the oxygen inflow mechanism should be used.

In making these recommendations, I do not advocate that premature babies be deprived of any necessary oxygen, only that oxygen not be given in excess of their needs. During the first 24 hours of life, when the death rate from prematurity is the greatest, oxygen in concentrations as high as 40 per cent can be given if necessary without fear of producing ocular lesions, provided that subsequent weaning is accomplished as quickly as the baby's condition permits. In institutions where these policies have been followed, the mortality or the morbidity has not increased.

The recommendation that oxygen should be used in treating the active disease has not been generally upheld. The disease has developed while babies were still in oxygen, and many have become worse in spite of treatment with oxygen. The good results reported by those who advised such treatment may be due to the tendency of RLF to undergo spontaneous arrest or regression in approximately 70 per cent of cases. I believe that by the time the first vasoproliferative changes have appeared in the fundus (usually between one and seven weeks of age) the ultimate fate of the eye already has been determined and from that time on any changes in the oxygen environment will have little or no effect on the final result. The critical period for oxygen control is during the earliest days of the premature baby's life.

The theory that too rapid withdrawal of oxygen is a primary factor in causing the disease also has not found general support, although some aspects of it may require further study. While sudden withdrawal of extremely high concentrations (for example, 50 to 70 per cent) conceivably might increase a tendency to retrolental fibroplasia, one can safely say that when oxygen is used in the concentrations recommended here, the earlier it is reduced and discontinued the less the chances of eye disease.

In spite of advances in preventive knowledge and their effectiveness, and in spite of the simplicity of the precautions required, cases of retrolental fibroplasia continue to occur. The responsibility of the individual physician is obvious. Leaders of medical societies and editors of medical journals have played their part in helping to bring recent knowledge before the profession. Now I believe that medical educators, public health authorities, hospital administrators and those responsible for hospital accreditation should give serious thought to *their* responsibilities in the prevention of this disease.

The problem can be given greater emphasis in the teaching curriculums of medical schools and nurses' training courses.

Public health authorities can issue directives to physicians and hospitals, as has been done with dramatic results in New York and Maryland. Because of frequent turnover of intern and nursing staffs, these directives should be prominently displayed in the nursery.

Hospital administrators can make sure the nurseries are adequately equipped to provide the extraordinary care needed in giving oxygen to premature babies. They can see that orders for oxygen are written as specific concentrations just as is done in ordering potentially toxic or lethal drugs, and that these concentrations are affirmed by the repeated use of an oxygen analyzer.

Finally, those responsible for hospital accreditation can, in the light of recent experience, underline the need for careful and controlled use of oxygen in the nursery and use their influence to safeguard against impaired vision or blindness in our babies.

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# Problems in Bleeding Disorders

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In few fields of medicine do the investigation and management of the patient present as many and as complex problems as in the study of bleeding disorders. These problems are encountered in all branches of medicine and are, thus, of general interest. It is the purpose of this article to discuss a number of such problems of practical importance, as we have met them in our clinical experience.

### *The Hemostatic Mechanism*

A working knowledge of the hemostatic mechanism seems indispensable to the understanding of bleeding problems. The concept shown in figure 1 is only a working hypothesis, although based on a series of well-established facts; it describes the sequence of events in traumatic bleeding. Hemorrhage occurs at the level of the metarteriole. As the vessel is severed, a fleeting, localized vasoconstriction takes place. Shortly afterward, platelets agglutinate at the site of injury. This physical phenomenon is followed by a more prolonged and more systemic constriction of all metarteriolar vessels, which is attributed to release of serotonin (5-hydroxytryptamine) from disintegrating platelets. Blood coagulation also seems to start at this time. Once fibrin has been formed, the clot begins to retract. The role of the fibrinolytic mechanism in this process remains to be fully evaluated.

Fibrin formation is perhaps the best-studied but most confusing step of this process. It appears to proceed through a series of phases, which may be reduced to three for purposes of description.[1] A platelet factor (thromboplastic factor) reacts with antihemophilic globulin (thromboplastinogen) to form thromboplastin, in the presence of other agents

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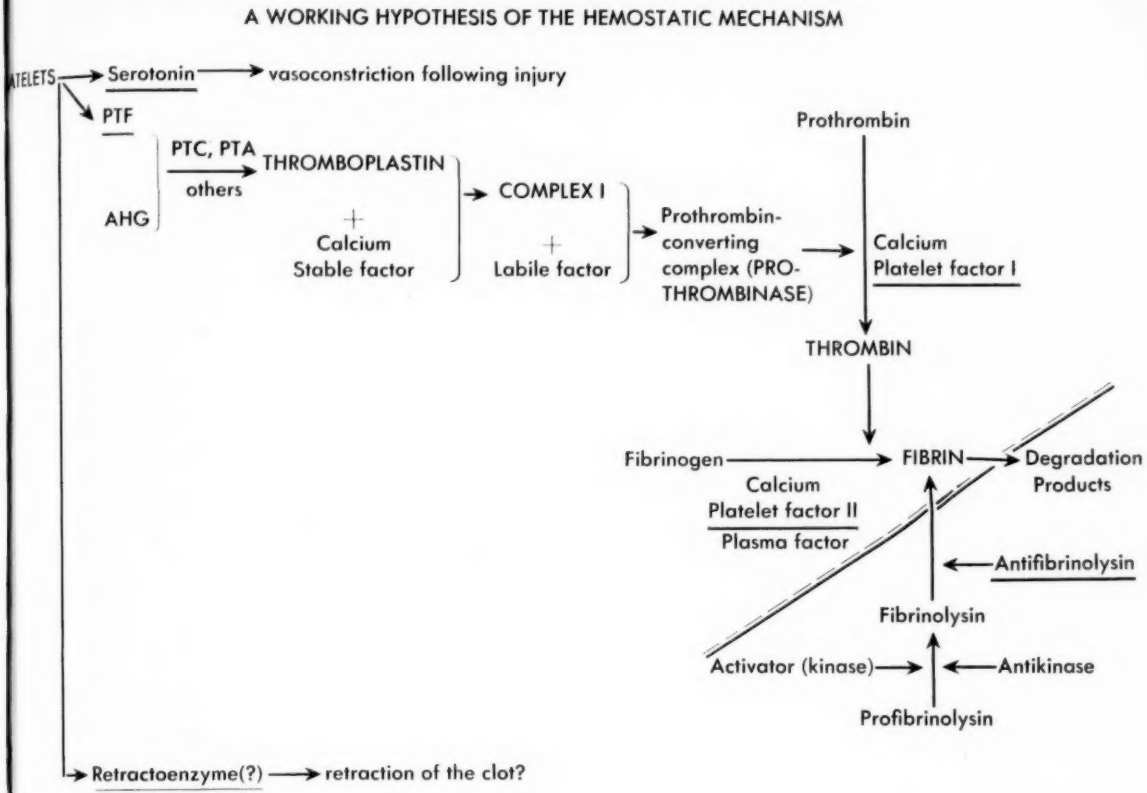



FIGURE 1. All factors of platelet origin are underlined. As the vessel is injured, a temporary, localized vasoconstriction follows. Shortly afterward, platelets begin to agglutinate at the site of the vascular injury. Their disintegration is followed by prolonged, generalized vasoconstriction (possibly due to release of serotonin). Almost immediately, blood coagulation process begins. The platelet thromboplastic factor (PTF) reacts with antihemophilic globulin (AHG) in the presence of plasma thromboplastin component (PTC) and plasma thromboplastin antecedent (PTA) to form thromboplastin. Thromboplastin reacts with the stable factor in the presence of calcium to form an intermediary complex (complex I or convertin); this, in turn, reacts with the labile factor to form a prothrombin-converting factor or prothrombinase. The latter converts prothrombin to thrombin in the presence of calcium, a reaction accelerated by a platelet factor. Thrombin forms fibrin from fibrinogen in the presence of an optimal amount of calcium, a reaction accelerated by the presence of a platelet factor and of an undefined plasma factor. Formation of thrombin is followed by a tremendous acceleration in fibrin formation, since thrombin causes greater disintegration of platelets and, thus, liberation of platelet thromboplastic factor. There also follows conversion of the labile factor to a serum accelerator (thereby greatly accelerating the conversion of prothrombin to thrombin) and, possibly, the activation of antihemophilic globulin from an inert precursor. Finally, platelets, either by their physical presence or by the liberation of a specific factor (retractoenzyme ?), cause retraction of the clot.

The fibrinolytic system is separated by a broken line, since it is not known whether or not this agent takes a part in the normal process of blood coagulation. An inactive precursor (profibrinolysin, plasminogen) is converted to the active enzyme (fibrinolysin, plasmin) by an activator (kinase) found in bacteria and tissues. The function of the activator is antagonized by an antikinase and that of fibrinolysin by an antifibrinolysin. Platelets represent an important source of antifibrinolysin, the content of which in serum and plasma is considerably diminished in thrombocytopenic states. Formed and activated fibrinolysin attacks fibrin (and possibly other coagulation factors) and liberates various degradation products.

(plasma thromboplastin component or Christmas factor, plasma thromboplastin antecedent and, possibly, others). Once thromboplastin, equivalent to tissue thromboplastin, has been formed, it reacts with calcium and stable factor (cothromboplastin, factor VII, convertin) to form an intermediate complex which, in turn, reacts with the labile factor (factor V, accelerin) to form a prothrombin-converting agent (plasma thromboplastin, prothrombinase). This then converts prothrombin to thrombin in the presence of calcium. As fibrinogen is acted on by thrombin, in the presence of an optimal concentration of calcium and a poorly defined factor found in plasma and serum, fibrin is finally formed. Agents supplied by platelets seem to accelerate the formation of thrombin and fibrin. This short description emphasizes that a normal hemostatic process is based on the integrity of three fundamental mechanisms: the vascular wall, the platelet and the coagulation of blood.

### *Detection and Classification of the Bleeding Patient*

A patient's history usually gives significant clues as to the presence of bleeding tendency. In the more severe cases there is history of spontaneous hemorrhage; in the less severe cases, bleeding follows only major injury or surgical and dental procedures. In both instances, the correct diagnosis and, therefore, the correct treatment require the use of laboratory procedures to confirm that a bleeding tendency exists and point out its most likely pathogenic mechanism. Table 1 indicates a number of tests which I consider indispensable to detect an important bleeding tendency. It is true that occasionally screening test results may be entirely negative but the patient still will bleed following trauma or surgery, and hemorrhagic disease will be discovered by more refined procedures than the screening tests. Such a situation, however, seems to be rare statistically. As shown in table 1, screening procedures not only detect the presence of a hemostatic defect, but also indicate whether it is due to vascular defect, platelet deficiency or coagulation abnormality. In the latter case screening procedures also indicate whether the hemostatic defect is due to poor formation of thromboplastin, thrombin or fibrin, respectively, or to the presence of circulating anticoagulants or fibrinolysis. More specialized technics may be needed, however, for a complete classification of the individual "bleeder." Thus, platelet count and its correlation with platelet function will distinguish between thrombocytopenia and thrombocytoasthenia. Special tests will reveal whether a state of thromboplastin deficiency is due to decreased concentration of antihemophilic globulin, plasma thromboplastin component, or plasma thromboplastin antecedent or to the presence of an antithromboplastic anticoagulant; and whether a state of hypoprothrombinemia is due to deficiency of prothrombin, stable or labile factor, or to the presence of a specific anticoagulant, etc.

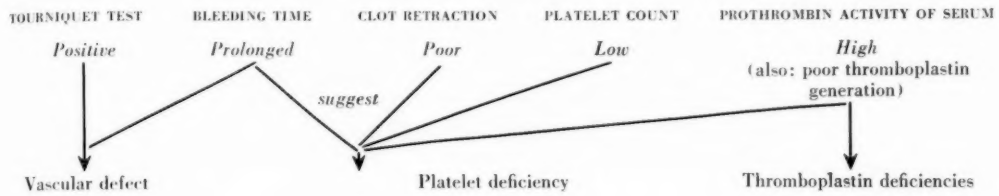
From a practical standpoint, screening technics are equally important in classifying known bleeders as well as in detecting a hemorrhagic tendency in presurgical patients. This fact is widely appreciated by surgeons; however, it is unfortunate that determination of bleeding and clotting times of whole blood is often considered sufficient to detect the patient who will bleed during surgery. This approach is obviously unsatisfactory as it even overlooks the tourniquet test, a very important and simple technic available to all.

A satisfactory positive-pressure technic for the tourniquet test is: The patient is placed in a reclining position. The cuff of a sphygmomanometer is applied to the arm and a pressure halfway between values of the patient's own systolic and diastolic blood pressure is maintained from 5 to 10 minutes, depending on the amount of discomfort and the patient's tolerance to it. Five minutes application is used routinely for women, and children under 14 years of age. At the end of the selected period of time the cuff is deflated and removed. Circulation is allowed to return to normal for approximately two minutes and the number of petechiae which have appeared in an area 2.5 cm. in diameter (approximately the size of a quarter) about 4 cm. below the antecubital fossa are counted. The development of no more than five petechiae in a man

TABLE 1

SCREENING AND MORE DETAILED TECHNICS FOR DETECTION AND CLASSIFICATION OF BLEEDING DISORDERS

SCREENING PROCEDURES




MORE SPECIFIC PROCEDURES

1. Direct microscopic observation of the capillary bed and study of its response to injury

2. Skin biopsy of the area of the elementary lesion

1. Morphologic study of the platelets

2. Determination of the activity of the single platelet constituents (serum serotonin level; determination of platelet factors I and II, determination of platelet thromboplastic factor)

3. Ability of the patient's platelet-rich plasma or isolated platelets to correct the defect of platelet-poor plasma in vitro (absent clot retraction; impaired prothrombin utilization during clotting, etc.)

4. Platelet agglutination tests

1. Determination of activity of antihemophilic globulin, plasma thromboplastin component, plasma thromboplastin antecedent, platelet thromboplastic factor

2. Correction of patient's coagulation defect by:
   a. fresh platelet-poor plasma: antihemophilic globulin, plasma thromboplastin antecedent deficiency

   b. serum: plasma thromboplastin component, plasma thromboplastin antecedent deficiency

   c. purified fraction I: antihemophilic globulin deficiency; purified fraction IV: plasma thromboplastin component deficiency; fresh deprothrombinized plasma: antihemophilic globulin deficiency

and 10 petechiae in a woman or child represents a normal result. Higher counts indicate increased vascular fragility. When the test is strongly positive, petechiae may also appear along the dorsal surface of the forearm and the hand. Increased vascular fragility may be found in: (1) cases of scurvy, vascular purpura of undetermined origin, senile purpura, etc. In these instances a positive test indicates the inability of the vessel wall to resist stress and pressure, a condition commonly attributed to improper amount and activity of "cement substance"; (2) thrombocytopenic purpura and thrombocytoasthenia, as indication of deficiency of platelets or platelet function. If the cuff is not properly applied or the patient does not keep the arm completely straight, petechiae may appear at the points of higher friction of the cuff on the skin. They also may be present along the area compressed by the lower margin of the cuff. Appearance of petechiae in these areas only is, thus, of little significance.

The tourniquet test is one of the simplest procedures to evaluate the hemostatic mechanism, and among the most valuable; it supplies information about both platelet sufficiency and vascular integrity. Its omission as a routine test appears, therefore, regrettable. Moreover, it may be said that, as carried out today, determinations of bleeding time and

TABLE 1 *(Continued)*

SCREENING AND MORE DETAILED TECHNICS FOR DETECTION AND CLASSIFICATION OF BLEEDING DISORDERS

SCREENING PROCEDURES

| PROTHROMBIN ACTIVITY OF PLASMA | FIBRINOGEN | LYSIS OF THE CLOT |
|---|---|---|
| *Low* | *Low* | *Present* |
| ↓ | *suggest* ↓ | ↓ |
| Hypoprothrombinemias | Fibrinopenic states | Fibrinolysis |

MORE SPECIFIC PROCEDURES

1. Quantitative determination of prothrombin, stable factor, labile factor

2. Correction of the low plasma prothrombin activity by the addition of:
   a. stored serum: stable factor deficiency
   b. stored plasma: prothrombin or stable factor deficiency
   c. fresh, deprothrombinized plasma: labile factor deficiency

1. Determination of profibrinolysin
2. Determination of antifibrinolysin

The determination of the clotting time of whole blood or of recalcified plasma should also be performed, if one suspects the presence of circulating anticoagulants. In this instance, the clotting time is delayed greatly if silicone-coated test tubes are used and not corrected by the addition of normal blood or plasma. As indicated in the table, the performance of the screening procedures indicates the presence of a hemostatic defect and roughly indicates its mechanism. Once the abnormal phase of the hemostatic process has thus been pinpointed, more selective procedures will usually define neatly the pathogenic mechanism of the hemorrhagic disease. In any case, the performance of any test should be preceded by careful history and physical examination, completed by other laboratory tests necessary to detect a primary disease, of which hemorrhage may be only a presenting symptom (leukemias, uremia, hypertension, etc.).

whole blood clotting time are of little value in predicting hemorrhage at surgery.

Bleeding time is most often determined by the so-called Duke technic, which consists of establishing the time required to arrest hemorrhage after the ear lobe has been pierced with a lancet under standardized conditions. The known variability of distribution of arterial and capillary vessels in this part of the body, however, makes the results of the test somewhat unreliable. It is not uncommon to notice striking differences in bleeding times of right and left ear lobes, one being entirely within normal limits and the other decisively prolonged, even when they are determined at the same time by the same technician. This is unfortunate since the bleeding time could be valuable in evaluating patients being prepared for surgery. It is the only available practical test of contractility of the vessels and it represents, in effect, a miniature surgical procedure which gives advance information on the severity of bleeding to be expected at actual performance of surgery. Correct performance of a bleeding time test becomes, then, a matter of considerable concern to the clinician and a simple, accurate technic would be highly desirable. Unfortunately, no ideal bleeding time test has been developed thus far. Ivy's technic,[2] as I have described it,[3]

obviates some of the causes of error, however, and is recommended for routine use.

*Ivy's technic*—The sphygmomanometer cuff is first inflated at 40 mm. Hg. After cleaning with absolute alcohol, the skin of the forearm is cut (2 mm. in length and depth) in an area 4 to 5 cm. below the antecubital fossa with a No. 11 Parker blade. Drops of blood which are formed are collected on filter paper every 30 seconds. Bleeding time is the period required for the hemorrhage to stop entirely. Under normal conditions, practically no blood oozes for the first 30 to 60 seconds due to the initial vasoconstriction, then oozing becomes copious for one to three minutes and finally stops fairly promptly in three to six minutes after incision of the skin.

The clotting times of whole blood and of recalcified plasma are currently used in many laboratories, although they are tests of doubtful value if not run with meticulous attention to details. The only instance where clotting time is of diagnostic value is, perhaps, in detecting circulating anticoagulants, either pathologically present or therapeutically administered (heparin). A criticism of clotting time of whole blood as a diagnostic procedure has been presented in a previous publication,[4] together with the description of a technic which overcomes some of its theoretical difficulties. When this technic is applied, however, the test becomes so cumbersome, involving so many careful details, as to be of limited practical value. For these many reasons, in my experience at least, the determination of the clotting time of whole blood, especially with the technics available today, is far from satisfactory. It appears more convenient, significant and informative to perform instead a one stage determination of the prothrombin time of plasma and serum or one of its many modifications. These tests have been greatly simplified by the availability of commercial reagents and have the advantage of giving a more realistic indication of the over-all coagulability of the blood as well as of the normality of the two phases of blood coagulation leading to the formation of thromboplastin and thrombin. Occasionally, however, even these technics may not be sufficient to detect a potential bleeder, and more complicated procedures may become necessary, such as the modified prothrombin consumption tests, the thromboplastin generation test, etc.

TABLE 2

MECHANISMS OF BLEEDING IN DISSEMINATED PROSTATIC CARCINOMA

THROMBOCYTOPENIA*

1. Invasion of the bone marrow by malignant cells (crowding out of megakaryocytes)
2. Production of platelet agglutinins and lysins (possibly through stimulation by an antigen common to malignant cells and to platelets)

FIBRINOGENOPENIA†
(and associated deficiency of other clotting factors)

1. Decreased synthesis of these proteins by tissues (direct replacement of tissue by metastasis; metabolic inhibition ?)
2. Increased destruction of fibrinogen, fibrin (and other proteins) by fibrinolysis
   a. Activation of fibrinolysin by prostatic "kinases"
   b. Passage into the patient's circulation of proteolytic substances of prostatic origin

*These mechanisms are common to all neoplastic processes with fairly extensive disseminations.

†These mechanisms are typical of disseminated prostatic carcinoma. Rarely, they may be encountered in other instances of disseminated neoplastic disease (cancer of bladder, breast, etc.).

Observation of clot retraction, detection of fibrinolysis and staining of a smear of peripheral blood for a semiquantitative appreciation of the number of platelets and the study of their morphologic appearance are procedures requiring little time and effort, but very rewarding either as presurgical tests or to classify a known bleeder.

### *The Occult Bleeder*

As mentioned already, the bleeder who has a definite family history and a well-defined history of previous bleeding ordinarily presents one major problem—classification of his hemorrhagic disorder (table 1), which is the key to successful treatment. Many therapeutic tools are available today and, if properly used, they can be counted on to control most bleeding disorders (table 2). The use of screening procedures is even more important in the

detection of the occult bleeder, i.e., the patient who does not present spontaneous bleeding but who will bleed severely at surgery or after trauma. Without screening procedures, the largest number of these patients are detected only after surgery. Most of them can be classified as having one of three different hemorrhagic syndromes: pseudohemophilia, thrombocytoasthenia and the hemophilialike diseases.

*Pseudohemophilia* is a bleeding diathesis due to inability of the metarteriolar vessel to contract following injury. Prolonged bleeding time is the only demonstrable abnormality of the hemostatic mechanism. The condition may be due to an intrinsic congenital abnormality of the vessel (vascular type) or to a qualitative deficiency of platelets limited to their inability to liberate serotonin (and, thus, a variety of thrombocytoasthenia). This disease has some interest for the obstetrician, since patients who have it do not develop any bleeding manifestations during pregnancy, apparently due to protection from placental hormones. After expulsion of placenta, however, they may present severe hemorrhage in the late puerperium.

*Thrombocytoasthenia* is a disease in which platelets are normal in number, but abnormal in function.[3] Platelets have abnormal morphologic appearance, appearing large and bizarre in stained preparations. From the physiologic viewpoint, as platelets influence clot retraction, prothrombin utilization during clotting, vascular fragility and contractility of the vessels, one may find evidence of isolated or multiple involvement of these various hemostatic functions of platelets (isolated or variously combined poor clot retraction, high prothrombin activity of serum, positive tourniquet test and prolonged bleeding time).

Equally important is a group of *hemophilialike syndromes*, which have been described along with classic hemophilia. These syndromes are characterized by normal plasma level of antihemophilic globulin and by the varying deficiency of newly detected factors, such as plasma thromboplastin component, plasma thromboplastin antecedent and, possibly, others. Determination of the serum prothrombin time will detect most of these conditions since deficiency of any of these factors leads to deficient formation of thromboplastin and, thus, to poor utilization of prothrombin during clotting. Unfortunately, the simple prothrombin consumption test may fail to detect a minor deficiency of these agents, although it may be important enough to cause bleeding during surgery or after trauma. Other technics are then needed, such as modified prothrombin utilization tests or the thromboplastin generation test, which are usually beyond the range of the clinical laboratory.

Once these bleeding states are recognized, severe hemorrhage after trauma or at surgery may safely be prevented. Thrombocytoasthenic states are, of course, controlled well, although temporarily (four to five days), by platelet transfusions. The bleeding time of pseudohemophilia may be considerably reduced, with corresponding decrease in bleeding tendency, by the prolonged administration of cortisone in large doses (150 to 200 mg. daily for 5 to 10 days). In case of emergency, intravenous administration of ACTH before, during and for 24 hours following surgical procedures may greatly reduce the severity of bleeding. Transfusion of fresh or stored plasma controls bleeding well in the hemophilialike syndromes, once these have been fully recognized and characterized.

### *More Specialized Problems*

*Poorly recognized causes of bleeding during surgery*—As surgery becomes more daring and more extensive, new causes for bleeding during and after surgery become known, even in patients whose hemostatic mechanism is otherwise entirely normal. Operative procedures requiring a large number of transfusions for blood replacement account for an increasing number of cases of excessive bleeding. Patients being operated on lose a considerable number of platelets through blood loss and utilization by the body for the control of bleeding. Bank blood supplied in return is, in most instances, platelet-poor. The patient may, thus, go into "*platelet debt*" and bleed as a result of thrombocytopenia, as seen during neurosurgical procedures or extensive

venous anastomotic operations (portacaval anastomosis, etc.). This bleeding tendency usually develops after loss and replacement of 8 to 10 pints of blood.* Investigation of the hemostatic mechanism at this point reveals prolonged bleeding time and drastic reduction of the number of platelets in the circulating blood. Whether or not prolonged bleeding time and increased clinical bleeding are directly due to platelet deficiency, the administration of platelets appears to control the hemorrhage. On the basis of this experience, I now administer transfusions of fresh blood, handled entirely through closed plastic systems, to patients whose loss of blood is considerable during surgery. These are properly spaced between the units of bank blood (one to each three or four units of bank blood). Administration of isolated freshly prepared or preserved platelets is equally effective. Similar considerations may be important in management of severe gastrointestinal bleeding, whatever its mechanism, when the patient may also go into platelet debt.

Another type of bleeding is that observed rather suddenly during operations on the chest, prostate, pancreas and uterus. In such instances, the procedure may be complicated by or followed a few hours later by explosive bleeding, at first localized to the area of surgery and, later, generalized. *Fibrinogenopenia* appears to be the most significant mechanism in these cases and it may follow either intravascular clotting (in which case the protein is used in the formation of fibrin) or fibrinolysis (which destroys fibrinogen as well as fibrin in vivo) or, more likely, a combination of both mechanisms. Lung, pancreatic, prostatic and uterine tissues contain agents possessing both thromboplastic and fibrinolysin-activating (kinasic) properties. The penetration of these agents in the patient's circulation is followed by fibrinogenopenia and bleeding. Controlling these conditions usually requires the combination of two procedures: the administration of fibrinogen to compensate for the loss of the protein and the administration of ACTH which seems to elevate plasma antifibrinolytic activity. It is imperative that these states be recognized and treated promptly since the patient's chances of recovery are considerably reduced if he is allowed to go into shock.

*Bleeding of obstetric accidents*—Abnormalities of the hemostatic mechanism occasionally develop in the course of obstetric accidents, such as severe toxemia of pregnancy and its complications, intra-uterine fetal death, meconium and amniotic embolism, premature separation of placenta, etc. The fundamental pathogenic mechanism of all these states is the penetration within the patient's circulation of materials of placental, amniotic or fetal origin, which possess at the same time thromboplastic and fibrinokinasic activity. As a result, thrombin is formed intravascularly, converting fibrinogen to fibrin and, at the same time, profibrinolysin is activated to fibrinolysin. This admittedly oversimplified hypothesis explains the severity of the fibrinogenopenia, due to depletion of fibrinogen by intravascular clotting, as well as its destruction by the fibrinolytic enzyme. The hypothesis is supported by many findings. Amniotic material within the veins and intravascular deposition of fibrin can be observed in autopsy or operative specimens. It is possible to reproduce some of the characteristics of fibrinogenopenia of obstetric accidents by the intravenous injection of thromboplastin in experimental animals.[6] Occasionally, the bleeding tendency of patients with fibrinogenopenia may be complicated by thrombocytopenia and by the appearance of a heparinlike anticoagulant. The latter frequently occurs in cases of meconium embolism.

As mentioned already, the fibrinogenopenia of these hemorrhagic states may be due to either intravascular clotting or fibrinogenolys-

*The reserve ability of the bone marrow to rush platelets into the circulation seems, in many cases, to prevent the occurrence of bleeding. Confirming this hypothesis is the appearance in the circulation of postoperative patients of large and bizarre platelets, like those seen in conditions of bone marrow hyperactivity and after hemorrhage. A complicating factor of bleeding in such cases is the possible deficit of labile factor and antihemophilic globulin which are also replaced only partially by stored blood. In patients with portal hypertension due to parenchymal liver disease undergoing venous anastomotic operations the deficient synthesis of these proteins by a diseased liver may further complicate labile factor and antihemophilic globulin deficiency.

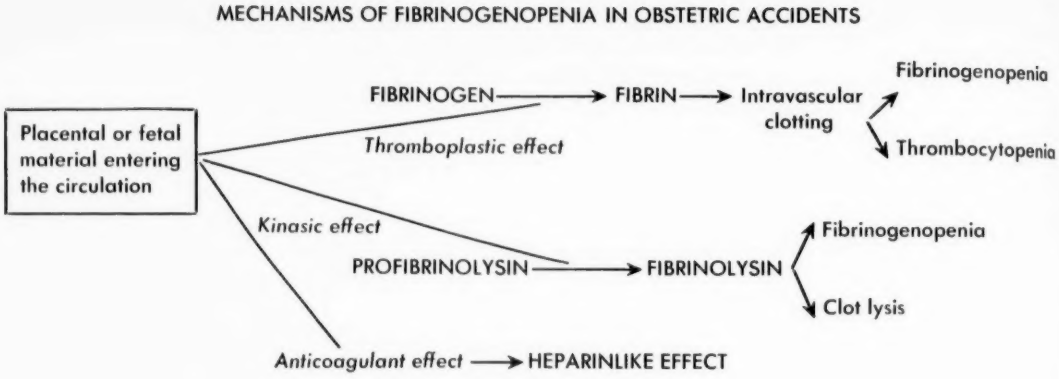



FIGURE 2. The entrance of placental or fetal material into the maternal circulation may be followed by a number of effects: (a) intravascular clotting, due to the thromboplastic effect of these materials. This occurs primarily in cases of premature separation of placenta, amniotic embolism, and toxemia of pregnancy; (b) fibrinolysis, with resultant destruction of fibrinogen in the circulation and any formed clot. This occurs primarily in accidents following miscarriages due to Rh incompatibility; (c) appearance of anticoagulant with heparinlike activity, which occurs in cases of meconium embolism.

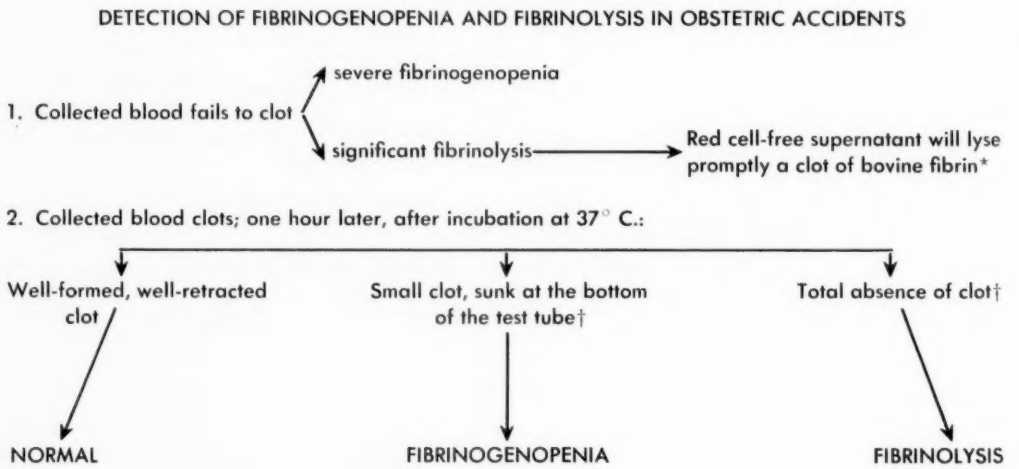

DETECTION OF FIBRINOGENOPENIA AND FIBRINOLYSIS IN OBSTETRIC ACCIDENTS
1. Collected blood fails to clot
severe fibrinogenopenia
significant fibrinolysis
Red cell-free supernatant will lyse promptly a clot of bovine fibrin*
2. Collected blood clots; one hour later, after incubation at 37° C.:
Well-formed, well-retracted clot
Small clot, sunk at the bottom of the test tube†
Total absence of clot†
NORMAL
FIBRINOGENOPENIA
FIBRINOLYSIS

FIGURE 3. *A clot is prepared by treating a solution of bovine fibrinogen with thrombin, and then washing repeatedly with distilled water to remove all traces of antifibrinolysin at the surface of the clot. This clot should be lysed if immersed in the patient's serum containing fibrinolysin. The patient's serum should be refrigerated until the test is run to prevent to a certain extent neutralization of fibrinolysin by antifibrinolysin.

†The presence of a small clot at the bottom of the test tube may easily be missed. It may be detected best by inverting the test tube over a sheet of filter paper. If the clot is present, although small, it will become easily visible. This test has only a relative value, since fibrinogenopenia and moderate fibrinolysis may be associated in the same patient. It has, however, a definite orientative value.

is in vivo. The respective roles of the two mechanisms seem to vary greatly from case to case, intravascular clotting being greatest in cases of intra-uterine fetal death (figure 2). As a rule, however, the two mechanisms are associated, although not of equal importance, and this consideration explains the need for a rather all-inclusive type of treatment. Purified fibrinogen is given liberally (from 2 to 10 gm.) to substitute for the loss of protein; ACTH is also given, intravenously (20 units) or intramuscularly (200 units in a single dose), in the hope of elevating the titer of antifibrinolysin. Both measures are usually fairly ineffective until the uterus is emptied of its content by either vaginal delivery or cesarean section, which eliminates the source of thromboplastic and fibrinokinasic material.

Recognition of this syndrome is based on the prompt appreciation of the presence of fibrinogenopenia and fibrinolysis. Several technics of varying degrees of complexity have been recommended. The obstetrician, harassed by the extreme emergency, will find the technic presented in figure 3 of some practical value.

*Bleeding tendency of polycythemic patients*—A particular problem is created by patients with polycythemia. In polycythemia vera, patients have an exaggerated tendency to thrombo-embolic manifestations, possibly due to the increased number of platelets. In addition, at times, they present a fairly severe bleeding tendency which makes them potential risks at surgery. The bleeding diathesis appears due to a combination of fibrinogenopenia (which I believe due to excessive use of the protein for erythropoietic needs) and the increased red cell mass. The combination of the two mechanisms causes the formation of a poor and friable clot. A similar problem is found in secondary polycythemia. Cardiac surgery for correction of congenital heart anomalies with cyanosis and secondary polycythemia, for example, has long been known to be accompanied by troublesome bleeding. Fortunately, it is possible to control easily the bleeding of the polycythemic patient or to prevent its occurrence altogether, should the patient come to surgery. Removal of two to three pints of blood and administration of two to three units of normal plasma are extremely effective. Venesection reduces the circulating red cell mass and administration of plasma supplies fibrinogen, thereby correcting the two basic mechanisms responsible for the bleeding tendency of these patients.

*Bleeding in disseminated prostatic carcinoma*—Severe cutaneous and mucosal bleeding may be observed in patients with disseminated prostatic carcinoma. The frequency of this complication is low (it occurs perhaps in 5 per cent of all cases), but its severity creates a most difficult therapeutic problem. The discovery of the relationship of prostatic carcinoma to a definite hemorrhagic syndrome has great clinical interest and represents one of the most interesting advances in the field in recent years.

Multiple mechanisms may induce bleeding in disseminated prostatic carcinoma (table 2). Bleeding may be due to severe thrombocytopenia as in other invasive neoplastic processes. This, in turn, is due to invasion of the bone marrow by malignant cells and crowding out of the megakaryocytes or to development of a platelet agglutinin. It is likely that the development of a platelet agglutinin is due to an antibody response against an antigenic substance common to the neoplastic tissue and the platelets. The presence of platelet agglutinins in the peripheral blood induces thrombocytopenia through a series of mechanisms which have previously been described.[7]

Another cause of bleeding is the depletion of such blood coagulation factors as fibrinogen, stable factor and prothrombin. This depletion may be due to decreased synthesis of these proteins by the liver through an unknown mechanism or to fibrinolysis. It is true that in a minority of these cases one can demonstrate the presence of fibrinolysin in the patient's circulating blood. It is commonly accepted that fibrinolysis in these patients either follows the activation of profibrinolysin by kinases delivered by the prostatic tissue or is due to the direct entry of proteolytic enzymes of prostatic origin into the patient's circulation. It is obvious that bleeding in patients with disseminated prostatic carcinoma re-

quires a careful evaluation of its possible causes. The corollary is also true: The possibility of prostatic carcinoma should be kept in mind when sudden bleeding develops in an elderly man.

Control of this type of bleeding is important and can usually be achieved by the administration of such substances as cortisone, stilbestrol and HYDROCORTONE®, which reduce the volume of the neoplastic tissue. In cases of emergency, the administration of large doses of ACTH or cortisone also seems to exercise a more direct effect on the bleeding manifestations, either by stimulating platelet production, or through a favorable effect on the vascular wall, or by decreasing the activity of fibrinolysis. This last effect is due to the interesting ability of ACTH and cortisone to increase either the production or the activity of antifibrinolysin. The prompt control of bleeding makes it possible to perform necessary surgical procedures, such as orchiectomy.

*Hemorrhagic diseases simulating surgical syndromes*—A few hemorrhagic syndromes may simulate serious surgical entities and create major management problems. Among them are hereditary hemorrhagic telangiectasia and acute anaphylactoid purpura (Schönlein-Henoch disease). *Hereditary hemorrhagic telangiectasia* is a potential cause of severe bleeding in the urinary and gastrointestinal tracts, and may go entirely unrecognized if the typical lesions of the skin and visible mucosa are overlooked or absent. It is important that skin and mucosa be explored carefully for the presence of telangiectasia in all cases when the source of gastrointestinal or urinary bleeding is not established with certainty. Many patients with this condition undergo surgery sooner or later, since bleeding, although intermittent, is repeated and severe. During surgery the bleeding site may be discovered. Unfortunately, the removal of a single intestinal tract or of one kidney where bleeding occurs is only a palliative measure. New lesions soon develop in the gastrointestinal tract or in contralateral kidney or pelvis. In my experience at least, the use of estrogenic hormones to treat this disease, as recommended recently,[8] has proved a failure.

*Anaphylactoid purpura* of the acute type, an acute capillaritis, may involve many organs or systems and, by the very multiplicity of its clinical manifestations, simulate any pathologic condition. When the intestinal tract is involved, severe abdominal pain and bloody diarrhea may lead to a diagnosis of intestinal intussusception, volvulus, etc. The presence of the typical skin lesions found in most cases of the disease and of hematuria (when the kidney is involved) may prevent unnecessary surgery. On the other hand, it should be kept in mind that intussusception may occur in acute anaphylactoid purpura, due to the strong contractions of the ileal viscus. Whether to operate is a decision which requires considerable experience and judgment.

### *Control of Bleeding by Specific and Aspecific Methods*

Bleeding disorders may be treated by local, specific or aspecific general measures. General measures have received greater attention since they are usually far more effective than local methods.

Table 3 summarizes procedures recommended for the specific treatment of hemorrhagic disorders. These procedures include administration of platelets in thrombocytopenic states and administration of the factor which is specifically lacking in various coagulation disorders (variously collected and prepared blood or plasma or a purified fraction). Specific measures also include administration of vitamin K and $K_1$, which are known to be indispensable for the synthesis of prothrombin; administration of ascorbic acid in the bleeding of scurvy; use of ACTH and steroid hormones, which affect favorably, although mysteriously, the resistance of the capillary wall. The value of local as well as of specific measures in the treatment of bleeding disorders has been reviewed in numerous recent publications (i.e., reference 7). Thus, this discussion is devoted primarily to the control of hemorrhage by a number of aspecific medications. The necessity of such discussion is obvious, since the use of some of these drugs has been advocated not only for the control of vascular purpura (a hemorrhagic diathesis for which other

TABLE 3

THERAPEUTIC MODALITIES IN THE TREATMENT OF HEMORRHAGIC DISEASES

PLASMA*

1. Fresh or freshly collected and frozen or lyophilized
   a. Hemophilia (AHG deficiency)
   b. Labile factor deficiency
   c. Bleeding of liver disease
2. Stored (within three weeks of collection)
   a. PTC and PTA deficiency
   b. Prothrombin and stable factor deficiency
   c. Fibrinogen deficiency

SERUM

1. PTC and PTA deficiency
2. Stable factor deficiency
3. Bleeding of liver disease

PLATELETS†

1. Idiopathic and secondary (hypoplastic, aplastic anemia; leukemia) thrombocytopenic purpura
2. Drug-induced thrombocytopenia
3. Thrombocytoasthenia

FRACTION I (fibrinogen + antihemophilic globulin)

1. Hemophilia
2. Fibrinogenopenia
   a. Congenital
   b. Acquired
      (1) Accidents of pregnancy
      (2) Fibrinolytic states

FRACTION IV

1. PTC deficiency
2. PTA deficiency

PROTHROMBIN CONCENTRATES‡

1. Prothrombin deficiency
2. Stable factor deficiency

VITAMIN K

1. Synthetic
   a. Hypoprothrombinemic states§
      (1) Congenital
      (2) Acquired
   b. Vascular fragility of liver diseases
2. Natural
   a. Hypoprothrombinemic states
      (1) Congenital
      (2) Acquired poisoning with DICUMAROL® and derivatives
   b. Vascular fragility of liver disease

FLAVONOIDS

1. Nonthrombocytopenic, drug-induced purpura
2. Senile purpura
3. Vascular purpura of diabetes
4. Hypertension
5. Malignancy
6. Similar conditions

PROTAMINE SULFATE

1. Hyperheparinemic states (severe radiation injury)

TOLUIDINE BLUE

1. Hyperheparinemic states (severe radiation injury)
2. Menorrhagia with uterine mucosa in secretory phase

ASCORBIC ACID

1. Purpura of scurvy

SPLENECTOMY

1. Idiopathic thrombocytopenic purpura
   a. Chronic variety
   b. Acute variety (with incontrollable bleeding)

SEMICARBAZONES, α-NAPHTHYLAMINES *(see text)*

*Freshly collected or stored whole blood may be used instead of plasma, if severe anemia is also present.

†Either as platelet-rich plasma or as platelet concentrates. The former form of treatment is usually more active.

‡At the present time, these concentrates are mixtures of prothrombin and stable factor.

§Complete correction of the hypoprothrombinemia by synthetic vitamin K is possible only if liver function is normal: in congenital hypoprothrombinemia, correction is possible only to an individual given level, over which, apparently, prothrombin synthesis cannot proceed.

AHG = Antihemophilic globulin.
PTC = Plasma thromboplastin component.
PTA = Plasma thromboplastin antecedent.

measures are poorly effective) but also for the control of bleeding in cases of platelet deficiency, coagulation disorders and during ordinary surgical procedures. Aspecific methods include the use of (1) flavonoids, (2) semicarbazones and α-naphthylamine derivatives, and (3) toluidine blue.

Vascular purpura is a generic term including a number of conditions in which bleeding is usually minor and the only positive laboratory finding, although not always present, is decreased capillary resistance (positive tourniquet test). Vascular purpura may accompany uremia, hypertension or diabetes; may follow ingestion of drugs; may be due to mechanical factors (orthostatic purpura, etc.);

or may be entirely idiopathic. The popularity of flavonoids depends to a certain extent on the lack of more specific methods of treating vascular purpura. In ordinary doses (approximately 130 to 300 mg. daily) such flavonoids as rutin and hesperidin are often helpful in management of the purpura of hypertension, diabetes and uremia. In those doses, however, they are of little value in any other type of vascular purpura. Such limitation is necessary since it is now generally understood that absorption of these drugs from the gastrointestinal tract is limited; that very high doses may be required for optimal therapeutic effect (such as 600 mg. daily for rutin); and that the activity of these drugs may be increased by their combination with ascorbic acid. Also, metabolites of rutin (like quercetin, which is probably a product of degradation of rutin in vivo) are therapeutically more effective than rutin or hesperidin. Only 30 to 50 mg. daily of quercetin may favorably affect the bleeding of vascular purpura.[9] Although flavonoids may be fairly ineffective at present, better evaluation of their use may modify the currently poor opinion of their role in treating vascular purpura.

Semicarbazones, pigment substances obtained by oxidation of epinephrine (adrenochromes, adrenoxyl, adrenoxin), are said to influence beneficially the bleeding time, primarily because they appear to inhibit degradation of serotonin.[10] This is thought to be one of the main factors influencing vascular contractility and thus the bleeding time. My experience with these agents has been unsatisfactory, since they usually fail to control the bleeding in pseudohemophilia, a disease which primarily affects vascular contractility. Occasionally, however, their use has successfully controlled capillary oozing from operative fields, as during tonsillectomy and prostatectomy. Even more fantastic claims have been made with reference to the hemostatic properties of some derivatives of α-naphthylamine. They are said to shorten bleeding and clotting times irrespective of the pathogenesis of the hemorrhagic syndrome. My experience with these agents has been entirely unsatisfactory.

Finally, considerable controversy has been created by the use of toluidine blue in the control of certain bleeding disorders. This drug, in proper dosage, neutralizes the effect of heparin in vivo and in vitro. Since Allen[11] claimed that heparinlike anticoagulants could be detected in the circulation of patients with radiation injury and other thrombocytopenic states, the drug has been used extensively in these conditions with disappointing results. Recently, however, the use of toluidine blue has been advocated to control excessive bleeding of functional menorrhagia and hypermenorrhea, especially if associated with an endometrium in secretory phase.[12-14] Maximum therapeutic effects are obtained with daily oral doses of 150 to 200 mg. This new therapeutic application of toluidine blue is interesting, but obviously requires more extensive clinical evaluation.

### *Summary and Conclusions*

1. Considerable progress in understanding the hemostatic mechanisms has been made in recent years. Accordingly, the detection of hemostatic abnormalities and their classification require more complete work-up than that usually employed in many hospitals and clinics. It is recommended that a series of screening technics be used for this purpose. These procedures are usually sufficient to detect a bleeding tendency even in the absence of history of previous hemorrhage. They are particularly important in the routine examination of candidates for surgery. Once the existence of a hemorrhagic tendency has been detected by screening technics, more refined procedures will establish the pathogenic mechanism of the hemorrhagic disease and, thus, its treatment. The routine determination of bleeding and clotting times only in preoperative cases gives a false sense of security, is often inadequate and is not recommended.

2. Particularly interesting to the surgeon are a number of hemorrhagic diseases in which bleeding usually only follows severe trauma or is first revealed during surgical procedures. These diseases include pseudohemophilia, thrombocytoasthenia and hemophilialike syndromes. They are usually recognized if proper screening technics are used.

3. Equally interesting are hemorrhagic syndromes which are the direct consequence of a surgical procedure and appear in patients whose hemostatic mechanism was normal prior to operation. One of these syndromes, thrombocytopenia caused by multiple replacement transfusions, is due to platelet deficiency induced by an abundant loss of blood and its replacement by platelet-poor bank blood. Administration of platelet-rich blood or of prepared platelets easily controls this type of bleeding. The other, fibrinolytic exsanguination, may occur during surgery on the lungs, prostate, pancreas or uterus and is due to the activation of the fibrinolytic system by tissue kinases or perhaps to intravascular clotting due to tissue thromboplastin entering the patient's circulation. Severe fibrinogenopenia develops, and the patient may be saved only by liberal administration of fibrinogen (to replace the loss of the protein being digested by fibrinolysin or used in the process of intravascular clotting) and ACTH (to raise the antifibrinolysin titer). Similar treatment can be used in hemorrhagic crises of obstetric accidents, as seen in toxemia of pregnancy, amniotic and meconium embolism, premature separation of placenta, etc. The bleeding in such cases is due to fibrinogenopenia, again because of the passage into the circulation of placental or fetal materials with thromboplastic and, or, fibrinokinasic activity. Finally, patients with polycythemia are also potentially serious bleeders and should be prepared carefully before surgical procedures.

4. The last part of this article discusses treatment of bleeding disorders. Particular attention is given to flavonoids, semicarbazones, derivatives of $\alpha$-naphthylamine and toluidine blue. Flavonoids offer some hope in the treatment of vascular purpura; toluidine blue is of some help in specific bleeding situations. Semicarbazones and $\alpha$-naphthylamine derivatives are of little or no value.

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# Operative Treatment of Uterine Prolapse

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FOR purposes of comparison, I have here three illustrations. The first represents the normal, or fairly normal, genitalia of a multipara. There is a little relaxation both anteriorly and posteriorly. The second illustration shows a moderate degree of cystocele but no prolapse. The bulge of the vaginal wall is apparent. The third slide demonstrates uterine prolapse. The cervix presents at the introitus, while anteriorly there is a well-developed cystocele.

Why do some women develop cystocele and uterine prolapse and others not? I cannot discuss all the many factors involved, but I will call your attention to a few pertinent ones.

Parity is a factor. In any large series the average parity of patients with uterine prolapse is about four. The patient's age generally is about 50 years. However, we see many women who have had half a dozen or more children, who are older than 50 and yet do not have prolapse.

Negro women ordinarily do not have prolapse of the uterus. Basically, then, we must introduce the factor of predisposition—that is, predisposition of tissue. Women who have good fascial muscle support probably will not develop either prolapse or lower perineal relaxation.

Retroversion possibly plays a role in the development of uterine prolapse. About 20 or 25 per cent of all women have retroversion.

Most patients with uterine prolapse complain that the feeling of "something protruding" is annoying. They may have some pelvic discomfort and be unable to empty the bladder without inserting a finger and pushing the

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uterus back into the body. They also may encounter difficulty emptying the rectum unless they introduce a finger and splint the posterior vaginal wall. Incontinence is a rare complaint, but stress incontinence may follow good anatomic repair; it is then that the patient may say, "Doctor, everything is wonderful, my prolapse is gone, but I cannot hold my water."

Sometimes these patients complain of leukorrhea, or they may seek medical help because of ulceration—they have examined themselves with a mirror and have seen an ulcer which they are sure is cancer; some bleeding may have been caused by the ulcer rubbing against the undergarments, and they are alarmed.

Prolapse of the uterus rarely interferes with coitus. Not uncommonly one sees young women with prolapse who become pregnant.

What can we do for these patients? If there are few complaints, if the prolapse is incomplete and if pregnancy is desired, perhaps it is best to do nothing. If one decides on operative treatment, there is a choice of procedures. Various factors influence the physician's decision as to which he will perform, including the patient's age and general nutritional state, her desire for a family, his familiarity and previous success with a particular procedure and, finally, his desire to improve his results through use of other types of operation. The final choice also will be influenced by the physician's decision as to the desirability of sacrificing the vagina or the uterus, or both.

Between the years 1928 and 1937, professional opinion regarding the choice of procedure for operative repair of prolapse of the uterus changed greatly. For instance, in 1928, vaginal hysterectomy was a rather uncommon procedure and Watkins' operation was very popular. By 1937, vaginal hysterectomy had attained almost its present-day popularity and the Watkins procedure was well on its way to becoming a historic curiosity. The Le Fort operation gained in popularity during that period, but has since lost favor. Such operations as Gilliam's and other procedures involving shortening of the round ligament, which, of course, are not indicated in treatment of uterine prolapse, have to a large extent now become of general historic interest only.

I would like to call attention to the Manchester (Fothergill) operation. Early in the period from 1928 to 1937 it was not performed at all. In the middle and late 30s it achieved some popularity which at present varies greatly. In some areas (e.g., Iowa City) it is performed rather frequently; in England it is still very popular.

Such operations as abdominal fixation were rarely performed, even during the late 30s.

Regardless of the choice of operative procedure, a few aspects of preoperative care come to mind. The woman with long-standing uterine prolapse frequently has a great deal of tissue edema, she may have ulceration and there may be passive congestion. Keeping her off her feet for a reasonable period will greatly relieve all three conditions. In addition, the postmenopausal patient generally is benefited, both preoperatively and in healing following surgery, by the administration of estrogens. Cystitis, if present in such a patient, may be treated adequately with the proper antibiotic. Constipation must be corrected and future stasis avoided. Thus, during preoperative management the patient will be more or less at bed rest for one or two weeks—but not entirely at bed rest, since this, too, may lead to undesirable sequelae.

If the physician decides to sacrifice the vagina, he may do the Neugebauer-Le Fort operation, colpectomy, or Goodal's partial colpocleisis. These operations are performed very rarely today but occasionally may be indicated in a case of an elderly woman with marked atrophy of the genital structures and no interest in marital relations. The latter may be difficult to judge; her interest may have waned but her husband's may not, and this much we owe to him.

An objection to the Neugebauer-Le Fort procedure is that it buries the uterus. Areas on the anterior and the posterior vaginal walls are denuded and joined together, thus producing an occlusion of the vagina except for a trough on either side to permit escape of any uterine secretion. The cervix cannot be visualized following this operation, and a pathologic process may develop which can-

not be observed readily or treated adequately.

Most physicians confronted with the decision as to choice of operative treatment of prolapse of the uterus prefer to sacrifice the uterus. This procedure removes a useless organ, generally, removes any uterine pathology and, most important, aids in reconstruction of the pelvic floor. We believe that better repair can be effected if the uterus is out of the way than if it is left behind.

One must consider the disadvantages of vaginal hysterectomy. Some women wish to menstruate as long as they are able. Sometimes a psychic disturbance follows the loss of the uterus; the patient may believe erroneously that she has lost her femininity. Another cited disadvantage is the problem of recurrence; removal of the uterus may make subsequent repair very difficult. Whether or not these objections are valid, we believe that uterine prolapse is best treated operatively by vaginal hysterectomy and plastic repair.

Once in a while we see a patient with uterine prolapse who does not want the uterus removed. It is mandatory, for example, to conserve the uterus if the patient desires pregnancy or to maintain menstrual function. Nor can we entirely discount the value of the uterus in reconstructing the pelvic diaphragm. It often provides a better support of the bladder, and if a recurrence should develop we have a little more to work with.

In view of the foregoing, the operation most commonly employed when the uterus must be preserved is parametrial fixation, the so-called Fothergill or Manchester operation. Our procedure is somewhat as follows: First we do a careful dilatation and curettage. If the cervix is long it is best to amputate it, but this is not essential if it is short and healthy. The principal part of the operation consists of reconstructing the parametrial tissue by plicating this tissue in front of the upper portion of the cervix. Although this procedure does preserve fertility, one may elect to perform the Manchester operation solely to preserve menstrual function. Furthermore, if children are not desired, one can do a vaginal tubal ligation at the same time.

For patients who need treatment but refuse surgery, we have recourse only to the use of a pessary. Hence, whether we like it or not, the pessary is still with us. I will only mention the common types of yesteryear: the hard rubber ball, the soft rubber doughnut, the hard rubber doughnut, and the cup and stem with a sling. We believe that if a pessary must be used, a properly fitted Gellhorn is the best. It has a few drainage holes which make it easier to keep clean, and it affords good support for the woman who is a poor surgical risk or who refuses operation.

In closing, I would like to emphasize that any gynecologist who is worthy of that name should not adjust the patient to his favorite operation but rather he should be capable of adjusting the operation to the particular needs of the patient.

# Concepts of Epidemiology of Sarcoidosis

## PRELIMINARY REPORT OF 1,194 CASES REVIEWED WITH SPECIAL REFERENCE TO GEOGRAPHIC ECOLOGY

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ALTHOUGH the clinical manifestations of sarcoidosis were first described 80 years ago, the cause of the disease remains obscure. After Hutchinson[1] first described the disease in 1875, Besnier[2] in 1889, Boeck[3] in 1899 and Schaumann[4] in 1917 each reported observations which more clearly defined certain clinical and pathologic features of the disease. Heerfordt,[5] and, more recently, Garland and Thompson,[6] and Longcope and Pierson[7] have made further contributions to the description of the disease.

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As sarcoidosis has become recognized more frequently in the United States, many reports have brought into clearer focus the criteria for diagnosis, but unfortunately they have shed little light on the cause of the disease.

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### *Etiology*

Sarcoidosis has been observed in many parts of the world. In Europe and particularly in Scandinavia, where the Negro population is low, the disease occurs more commonly in the white race. In the United States, on the other hand, the disease occurs more commonly in Negroes. However, no cases of the disease have been reported from Negroid Africa, which may only reflect a lack of familiarity with or a lack of interest in the disease on that continent.

The disease has been observed in children and in the aged, but its onset occurs most frequently between the ages of 20 and 40 years. Both sexes appear to be affected with equal frequency, although various reports disagree on this point.

Many clinicians have argued that sarcoidosis is a manifestation of tuberculosis because the lesions resemble miliary tubercles histologically. They also point out that patients with sarcoidosis not infrequently die of tuberculosis. However, the rarity of demonstra-

tion of tubercle bacilli within the lesions and the frequent occurrence of negative skin reactions to tuberculin (60 to 70 per cent) would tend to disfavor the argument that the disease is a manifestation of tuberculosis.

Those who believe that sarcoidosis is not related to tuberculosis argue that the absence of caseation necrosis makes it most unlikely that the disease is due to *Mycobacterium tuberculosis*. Many other theories as to the cause of the disease have been advanced and considered. Leprosy, brucellosis, syphilis, and infections due to viruses, fungi, protozoa and helminths have been considered to be inciting causes, but no definite proof has been advanced to support these hypotheses. Concepts of the cause of the disease have been reviewed by Jacques[8] and Longcope.[9]

More recently, the similarity of sarcoidosis to berylliosis and to histoplasmosis has been described.[10,11] Refvem[12] analyzed tissue obtained from patients with sarcoidosis and suggested that calcareous spar found in certain soil types may be a possible etiologic agent. He also demonstrated that quartz particles and other foreign bodies may provoke localized sarcoid formation. Refvem's studies also led him to suggest that the epithelioid cell formation occurs when the primary irritant is an antigen capable of stimulating antibodies which contain or accumulate phospholipid.

### *Epidemiology*

It has been most difficult to determine the true incidence or prevalence of sarcoidosis since most reports in the literature deal with small numbers of cases usually seen in hospitals situated in large cities. Freiman[13] in 1948 reviewed the literature and suggested that there were more than 1000 cases of sarcoidosis in the United States. Since recognition of the disease may be difficult, its true incidence is undoubtedly much higher than presently suspected.

After the observation of Dr. John Ransmeier[14] of the National Research Council that sarcoidosis occurred predominantly in military personnel from the southeastern part of the country, Michael and his associates[15,16] made an intensive epidemiologic study of the disease. They reviewed the records of 350 veterans who had sarcoidosis during World War II, and confirmed the fact that most of these patients were born in the southeastern part of the United States. The birthplaces were strikingly rural especially when population densities were considered. The incidence of the disease in Negro veterans was 20 times as great as it was in white veterans when calculated by number of instances of the disease per 100,000 inductees. These authors suggested that the environment of the area in which the disease was endemic might be responsible for the geographic distribution, and they postulated that the distribution could be related to the type of soil predominant in the southeastern part of the United States.

The Veterans Administration provides a unique opportunity for case record studies since within its large system of hospitals one may have available large numbers of cases of even relatively rare diseases. The excellent follow-up facilities of the Veterans Administration make it possible to evaluate the natural history of the disease and also provide an opportunity to review the diagnostic criteria applied in each individual case.

The present report is based on a study of 1,194 cases in which a diagnosis of sarcoidosis was made in 172 Veterans Administration hospitals between 1949 and 1954. Information concerning age, race, sex, occupation, place of birth and place of initial hospitalization was reviewed in an effort to detect epidemiologic patterns which might afford clues to the cause of the disease.

The geographic distribution of the birthplaces of the patients was studied not only to compare it with the distribution in the cases reported by Michael and his co-workers,[15,16] but also because it was believed that this represents clues to possible etiologic agents.

Figure 1 shows the distribution (by place of birth) of the 1,194 veterans. It not only confirms the geographic distribution reported by Michael and his associates[15,16] but it also shows that the disease occurred in a significant number of white veterans who were born in New England and in the North Central states. This extends the distribution pattern

FIGURE 1. Geographic distribution of birthplaces of 1,194 veterans with sarcoidosis.

of the disease to areas of the United States in which the disease was not found to be endemic by these authors.

As an aid in determining the major residence of these patients, we also studied the place of hospitalization. This also was done in order to determine whether or not the diagnostic criteria varied between the widely scattered Veterans Administration hospitals.

The hospitalization rate for white World War II veterans with sarcoidosis was 3.3 per 100,000 and that for the Negro veterans was 40.1. The birthplaces of the white veterans affected, expressed in the order of decreasing frequency, were as follows: Connecticut, Rhode Island, Georgia, Arkansas, North Dakota, Minnesota, Massachusetts, Alabama, Maine and Virginia. A preponderance of the Negro veterans were born in the Southeast. An analysis of the birthplaces of these veterans reveals that the prevalence of sarcoidosis is somewhat higher in rural than in urban communities. This is particularly true in the southeastern states where there are a number of small communities which were the birthplaces of more than one of the patients.

The ages of the 1,194 patients at the time of onset of the sarcoidosis are not known. At the time these patients were admitted to the hospital because of sarcoidosis, 90 per cent of them were less than 44 years of age and at least 60 per cent were less than 34 years old. Of all patients who were admitted to Veterans Administration hospitals during the same period, 54 per cent were more than 44 years of age and 36 per cent were less than 34 years old. The Negro veterans with sarcoidosis were younger than the white veterans who had this disease.

A comparison was made between the occupations of the veterans who were admitted to the hospitals because of sarcoidosis and the occupations of those admitted for the treatment of other conditions. Although certain differences in occupations were noted, they were not striking enough to be conclusive. An

attempt now is being made to study further the complete occupational and residence histories of some of the patients with sarcoidosis.

### *Material*

An analysis of the clinical features observed in 80 of the 1,194 cases has been made to determine whether or not significant clinical differences occur in various sections of the United States. In addition, this analysis gave us an opportunity to evaluate the diagnostic criteria utilized in widely scattered hospitals.

The criteria for diagnosis used in this review are those defined by a Subcommittee of the National Research Council in 1948.*

An effort was made to sharpen the application of these criteria more critically by separating the cases into three major categories: (1) those in which the diagnosis was made by biopsy or by the examination of material obtained at autopsy; (2) cases in which commonly recognized clinical and laboratory manifestations of the disease were present, and (3) cases in which the clinical and roentgenographic findings warranted a diagnosis of sarcoidosis although the laboratory findings were not significant. These diagnostic criteria were fulfilled in 74 (92.5 per cent) of the 80 cases. The remaining 6 cases (7.5 per cent) were excluded from further consideration. Table 1

*"Sarcoidosis is a disease of unknown etiology, characterized pathologically by epithelioid tubercles, with inconspicuous or no necrosis, occurring in any organ or tissue, and by the frequent presence of tubercles. The lesions may be replaced by fibrosis, hyalinization or both.

"Clinically the lesions may be widely disseminated. The tissues most frequently involved are lymph nodes, lungs, skin, eyes and bones (especially of the extremities). The clinical course is usually chronic with minimal or no symptoms. However, there may be acute phases, characterized by malaise and fever. There may be symptoms which are referable to the tissues and organs involved. The tuberculin test is frequently negative. Plasma globulin is often increased.

"The outcome may be clinical recovery without gross or radiologically visible residuals, or it may be impairment of the function of the organs involved, or a continuous chronic course of the disease."

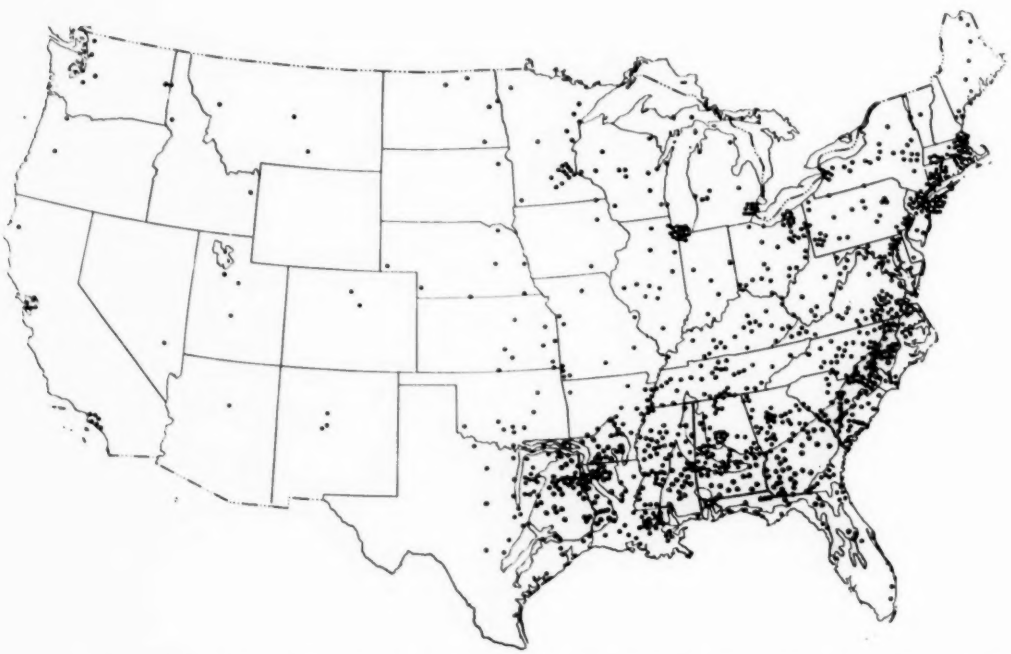

FIGURE 2. Geographic distribution of birthplaces of 1,194 veterans with sarcoidosis superimposed on map showing red-yellow podsolic soils of the middle coastal plain.

TABLE 1

DIAGNOSTIC CRITERIA AND RACE OF PATIENTS

| DIAGNOSTIC CRITERIA | CASES | RACE | |
|---|---|---|---|
| | | *White* | *Negro* |
| Diagnosis made by biopsy or autopsy | 55 | 35 | 20 |
| Commonly recognized clinical and laboratory manifestations | 9 | 6 | 3 |
| Characteristic clinical and roentgenographic findings | 10 | 8 | 2 |
| TOTAL | 74 | 49 | 25 |

shows the number of cases in which the various defined diagnostic criteria were fulfilled.

### *Race and Sex*

Forty-nine of the 74 patients were white veterans and 25 were Negroes (table 1). The preponderance of white over Negro patients in a ratio of approximately 2:1 may be partially attributable to the selection, for the initial review, of only those patients who were admitted to hospitals situated outside of the area of geographic concentration of sarcoidosis in the United States, namely, the Southeast. Five of the veterans in these cases were women; three of the women were white and two were Negroes.

### *Age*

At the time of their initial hospitalization for sarcoidosis, 27 (55 per cent) of the 49 white patients and 21 (84 per cent) of the 25 Negro patients were under 31 years of age (table 2). Other authors have reported that the disease occurs most frequently in persons who are between the ages of 20 and 40 years. However, in our series of cases, the disease occurred more frequently among Negroes who were less than 26 years of age than it did among white veterans who were of the same age. In our small series of cases, none of the Negro patients were more than 35 years old whereas eight (16 per cent) of the white patients were beyond this age.

### *Biopsy*

In 55 of the 74 cases, biopsy disclosed the presence of sarcoidosis. In these 55 cases, the results of biopsy were positive on 76 occasions. It is interesting to note the high percentage of cases in which biopsy was performed since a clinical diagnosis of sarcoidosis is difficult to confirm. Table 3 shows the sites from which the specimens were obtained. On 68 (89 per cent) of the occasions in which the result of a biopsy was positive, the specimen was obtained from the lymph nodes, liver, lung or skin. On the remaining eight occasions (11 per cent), the specimens were obtained from the parotid gland, tonsillar tissue, endobronchial mucosa or the gastrocnemius muscle.

TABLE 2

AGE OF PATIENTS AT TIME OF FIRST HOSPITALIZATION FOR SARCOIDOSIS

| AGE, YRS. | ALL PATIENTS | | WHITE PATIENTS | | NEGRO PATIENTS | |
|---|---|---|---|---|---|---|
| | *Number* | *Per cent* | *Number* | *Per cent* | *Number* | *Per cent* |
| Under 26 | 24 | 32 | 10 | 20 | 14 | 56 |
| 26 to 30 | 24 | 32 | 17 | 35 | 7 | 28 |
| 31 to 35 | 18 | 25 | 14 | 29 | 4 | 16 |
| 36 to 40 | 3 | 4 | 3 | 6 | 0 | 0 |
| Over 40 | 5 | 7 | 5 | 10 | 0 | 0 |
| | 74 | 100 | 49 | 100 | 25 | 100 |

TABLE 3

SOURCE OF SPECIMENS ON 76 OCCASIONS ON WHICH BIOPSY DISCLOSED SARCOIDOSIS IN 55 CASES

| SOURCE OF SPECIMENS | OCCASIONS | |
|---|---|---|
| | *Number* | *Per cent* |
| Lymph nodes | 36 | 47 |
| Liver | 12 | 16 |
| Lung | 10 | 13 |
| Skin | 10 | 13 |
| Other sites | 8 | 11 |
| | 76 | 100 |

TABLE 4

SITES OF INVOLVEMENT IN 74 CASES OF SARCOIDOSIS

| SITES OF INVOLVEMENT | CASES | |
|---|---|---|
| | *Number* | *Per cent* |
| Lungs, including the hilar lymph nodes | 71 | 96 |
| Other lymph nodes | 54 | 73 |
| Liver | 16 | 22 |
| Skin | 11 | 15 |
| Eyes | 10 | 14 |
| Spleen | 10 | 14 |
| Heart, kidneys, bone, central nervous system and parotid gland | 2 | 3 |

TABLE 5

SYMPTOMS IN 74 CASES OF SARCOIDOSIS

| SYMPTOMS | CASES | |
|---|---|---|
| | *Number* | *Per cent* |
| Cough | 46 | 62 |
| Loss of weight | 32 | 43 |
| Dyspnea | 21 | 28 |
| Fatigue | 20 | 27 |
| Chest pain | 17 | 23 |
| Visual disturbances | 8 | 11 |
| None | 5 | 7 |

### *Sites of Involvement*

Table 4 shows the sites of involvement in the 74 cases. Roentgenographic examination revealed that the lungs and the hilar lymph nodes were involved in 71 (96 per cent) of the cases. The right paratracheal lymph nodes were involved in a significant number of cases. In three cases, the disease was localized and involved only the skin.

### *Symptoms*

Symptoms related to sarcoidosis were present in all but five (7 per cent) of the 74 cases (table 5). The most frequent symptom was cough. In most of the cases, the cough was nonproductive and occurred either in the morning or at night. In cases in which the cough was productive, the sputum was described as being thin and mucoid, and white to yellow in color. Occasionally, a paroxysm of coughing caused hemoptysis, emesis or "blackout spells." Loss of weight, which was considerable in many cases, was the next most frequent symptom. Other symptoms included dyspnea, fatigue, chest pain and visual disturbances. In several cases, the symptoms first occurred or increased in severity after the patients were told that a chest roentgenogram, which was made in the course of a routine physical examination, was abnormal.

### *Tuberculin Test*

Schaumann[4] said that he never has observed a case of uncomplicated sarcoidosis in which the result of a tuberculin test was positive. Other authors have reported that positive tuberculin reactions, although of a minor degree, are obtained in as many as 40 per cent of cases of sarcoidosis. A tuberculin test was performed in 66 of the 74 cases in our series. It was negative in 44 (67 per cent) of these 66 cases, including 30 (70 per cent) of 43 cases in which the patients were white veterans and 14 (61 per cent) of 23 cases in which the patients were Negroes.

### *Kveim Reaction*

Considerable interest was aroused by Kveim's report[17] of the production of an unusual cutaneous reaction in patients with sarcoidosis by the intracutaneous injection of heated saline suspensions of tissues obtained from patients with active sarcoidosis. Nelson[18] reported 24 cases of sarcoidosis and said that the Kveim reaction was positive in 11 of the 15 cases in which the disease was in the active phase. The Kveim reaction was performed in 10 of the 74 cases in our series, and it was positive in 5 of these 10 cases.

### *Proteinemia*

Salvesen[19] was the first to point out that the value for the serum protein may be abnormally high in cases of sarcoidosis. The values for the total serum protein and the albumin-globulin ratio of the serum were determined in 68 of the 74 cases in our series. In 21 (31 per cent) of these 68 cases the value for the total protein was higher than 7.9 mg. per 100 ml. of serum, and in 61 (90 per cent) of the cases the albumin-globulin ratio of the serum was less than 2:1. Other authors have reported that the value for the serum protein is 8 gm. or more in almost one-third of all cases of sarcoidosis. The hyperproteinemia usually is due to an increase in the serum globulin.

### *Serum Calcium*

Moderate degrees of hypercalcemia have been reported by other authors. The value for the serum calcium was determined in 42 of the 74 cases, and it was higher than 11 mg. per 100 ml. of serum in 17 (40 per cent).

### *Serum Alkaline Phosphatase*

Significant increases in the value for the serum alkaline phosphatase have been reported by other authors. The value for this enzyme was determined in 20 of the 74 cases. In 6 of the 20 cases, it was higher than 5 Bodansky units per 100 cc. of serum.

### *Leukopenia*

In one-fourth of the 74 cases, the leukocyte count was reduced sufficiently to constitute a moderate leukopenia. In 9 (36 per cent) of the 25 Negro patients, it was less than 5000 per cubic millimeter of blood. Leukopenia also occurred in 9 (18 per cent) of white patients.

### *Eosinophilia*

The most frequent change disclosed by a differential leukocyte count was an eosinophilia. An increase in the eosinophils to 7 per cent or more occurred in one-sixth of the 74.

### *Other Laboratory Findings*

No striking alterations were observed in the values for the blood cholesterol or blood sugar. The sedimentation rate of the erythrocytes was increased in most of the cases. Bence Jones-like bodies were found in the urine of one.

### *Comment*

The high prevalence of sarcoidosis in veterans who were born in the eastern part of the United States and the preponderance of cases in which the patients were born in rural areas of the Southeast present an opportunity for speculation concerning the etiologic factors. It is tempting to make ecologic correlations based on this geographic distribution.

It is evident that the geographic distribution of the birthplaces of the patients in our entire series of 1,194 cases does not fit the pattern of sandy soil distribution noted by Gentry, Nitowsky and Michael[16] (figure 2). A closer correlation exists between the distribution of the birthplaces of the patients in our series of 1,194 cases and the distribution of forests in the United States. There is a close correlation between the birthplaces of these patients and the distribution of forests (figure 3). It is not unreasonable to consider that forest products or even diseases of plant life are related in some way to sarcoidosis. If one considers that sarcoidosis is a form of pneumoconiosis, the possibility that certain forest products may incite the granulomatous reaction that is characteristic of this disease is not completely fanciful. On the other hand, those who believe that sarcoidosis is an infectious disease may be attracted by the suggestion that fungi or viruses occurring in plant life may be responsible for the disease in man.

Further correlation may be made with the climatic conditions in the United States. In nearly all of the entire series of 1,194 cases, the patients came from nonarid sections of the country. Figure 4 reveals an interesting correlation between the birthplaces of the patients and the nonarid sections of the United States.

An analysis of the clinical records in 80 of the entire series of 1,194 cases of sarcoidosis in which the patients were observed in widely scattered Veterans Administration hospitals indicates that the diagnostic work-up was sufficiently comparable so that only six cases (7.5 per cent) had to be excluded from fur-

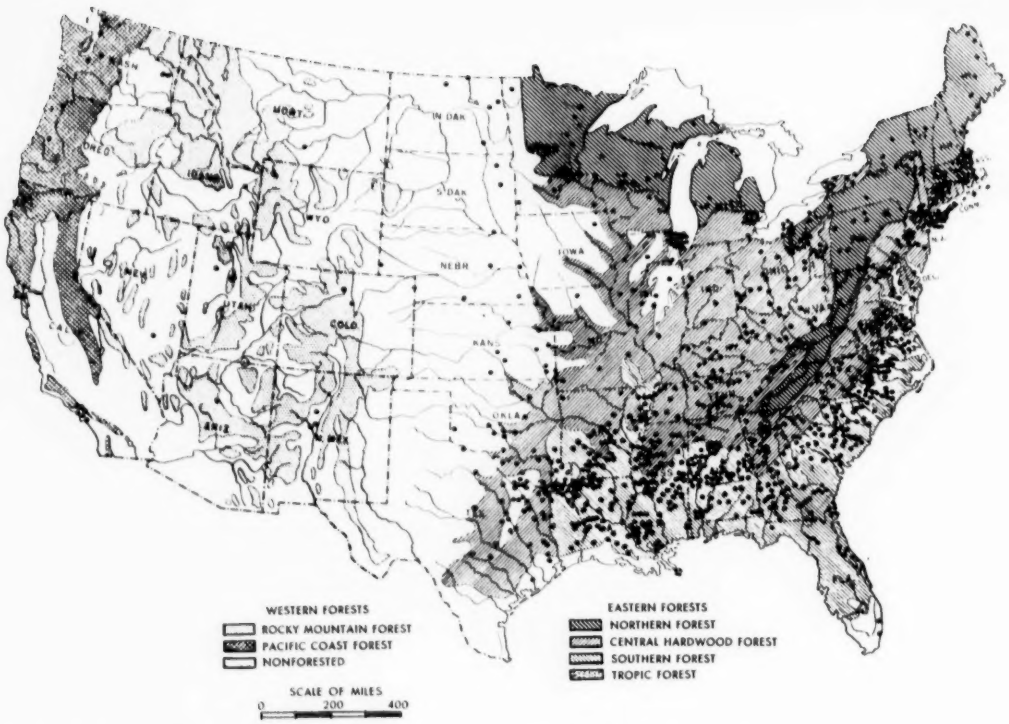


FIGURE 3. Geographic distribution of birthplaces of 1,194 veterans with sarcoidosis correlated with distribution of forests in the United States.

ther consideration because of inadequate diagnostic criteria. We, therefore, do not feel that a bias exists owing to unusual interest in sarcoidosis in one particular part of the country.

The finding of the disease in Negroes at an earlier date than in white veterans suggests several possible explanations. Negroes may be more susceptible to the causative agent of the disease and thus manifest clinical symptoms more readily than white persons. Another possibility is that the social and economic environment of Negroes brings them into closer and perhaps more frequent contact with the etiologic factors at an earlier age. The hospitalization rate for Negro veterans with sarcoidosis was 12 times greater than that for white veterans with this disease. This, however, does not account for the geographic distribution of the birthplaces of the patients, since only a few were born in certain northern states with a relatively large Negro population.

There are two striking differences in the geographic distribution of the birthplaces of the veterans in our series of cases and in the distribution of the birthplaces of the servicemen in the cases reported by Gentry, Nitowsky and Michael. Practically none of their servicemen were born in two areas in which many of the veterans in our series of cases were born. Although a few of their servicemen were born in the Mississippi delta, a significant number of the veterans in our series were born in this region. This difference at once raises doubts about the assumption of these authors that soil was a controlling influence. Their selection of soil as the most important ecologic factor apparently was based on their observation that the incidence of the disease was low among men born in the Mississippi delta.

Many of the veterans in our series of cases

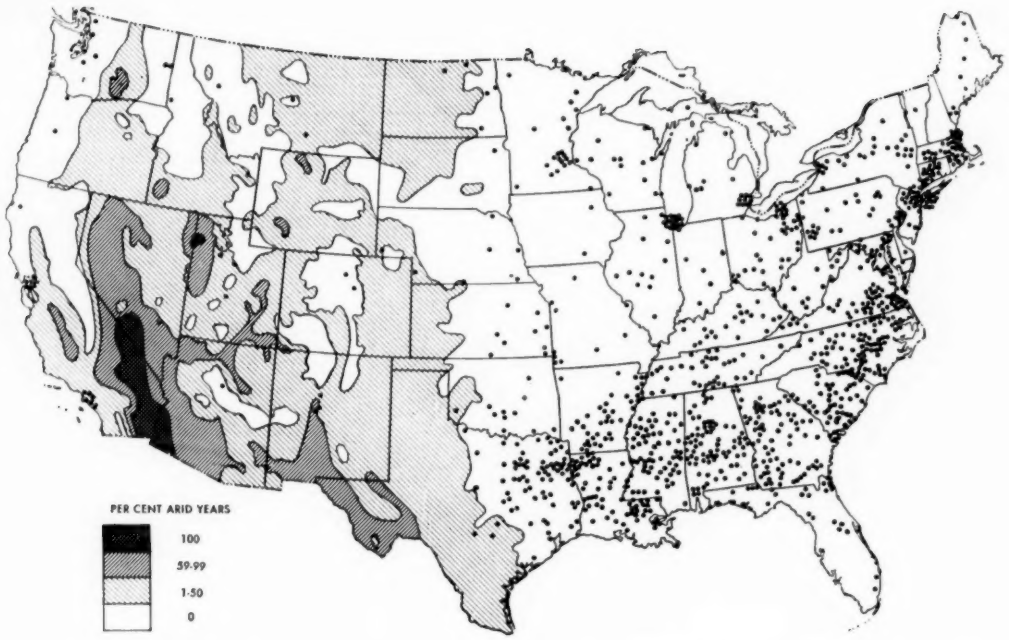


FIGURE 4. Geographic distribution of birthplaces of 1,194 veterans with sarcoidosis correlated with nonarid sections of the United States.

were born in New England, but very few of the servicemen in the series of Gentry, Nitowsky and Michael were born in this region. The small number of these servicemen who were born in New England strengthens the soil hypothesis, but the great number of veterans in our series who were born in this region weakens this hypothesis. In some of the cases in each series, the patients were born in an area along the Erie Canal. This does not strengthen the soil theory, but it may be used in support of broader ecologic concepts.

The heavy distribution of the birthplaces of Gentry, Nitowsky and Michael's servicemen in the southeastern part of the country would cover both the New England region and the region of the Erie Canal if one adds the ecologic factors of humidity, crops and forest distribution. The difference in the distribution of the birthplaces in the Mississippi delta in the two series of cases may not require any additional comment, but the differences in New England and in the North Central states may require further explanation.

In the cases reviewed by Gentry, Nitowsky and Michael, the patients were servicemen at the time the diagnosis was made, that is, prior to 1946. In our series of cases, the patients were veterans, and the diagnosis was made in the years 1949 to 1954, in some instances, about a decade later than in the cases reviewed by Gentry, Nitowsky and Michael. In both groups, however, the patients were products of Selective Service and, therefore, were from the same stratum of society. The only difference that is certain and measurable is that of time. Such a difference could be correlated with other differences in these two groups of cases in several ways.

If a long incubation period is postulated, the high distribution of the birthplaces of our veterans in New England could be accounted for if the veterans who had been born in this region had served in the Southeast where the

disease is endemic. This is supported in part by the older age incidence of the disease among the white veterans who were born in New England as compared with the age incidence of the disease among Negroes who were born in the South.

In the decade that elapsed between the time of diagnosis in the two series of cases, there may have been ecologic changes that resulted in shifts of etiologic factors. Although this difference in time probably did not have any effect on the etiologic role of the soil, it is possible that it did have some effect on such ecologic factors as humidity, crops and plant life. There was no shift to arid regions.

### *Summary*

The present report is based on a review of 1,194 cases of sarcoidosis seen in 172 Veterans Administration hospitals between 1949 and 1954. Information concerning age, race, sex, occupation, place of birth and place of initial hospitalization was reviewed in an effort to detect epidemiologic patterns which might afford clues to etiology.

The hospitalization rate for white World War II veterans with sarcoidosis was 3.3 per 100,000 and 40.0 for Negro World War II veterans. The comparative rates of sarcoidosis of white World War II veterans by birthplace revealed that the highest hospitalization rates occurred among veterans born in Connecticut, Rhode Island, Georgia, Arkansas, North Dakota, Minnesota, Massachusetts, Alabama, Maine and Virginia, in order of decreasing frequency. The hospitalization rates for Negro veterans was 20 times greater than for white veterans, and showed a preponderance of patients born in the Southeast.

Study of the birthplaces of all veterans extends the distribution pattern of the disease to areas of the United States not previously considered to be endemic. Correlation between the distribution of sarcoidosis in veterans with certain ecologic factors suggests that some aspect of the forest distribution in the United States may be an important environmental factor responsible for the geographic concentration of the disease.

We are indebted to Dr. William S. Middleton for emphasizing to us that the idea that sarcoidosis occurred predominantly among military personnel who came from the southeastern part of the United States, which first was noted by Ransmeier and reported by Michael, Cole and Beeson,[15] lacked confirmation. This stimulated us to make the present study, to which Dr. Middleton gave his support and has made many helpful suggestions.

Once the study was inaugurated, we received both encouragement and disillusionment from the accuracy and objectivity with which Mr. Jack Williams of Reports and Statistics Service analyzed race, occupation, birthplace, population densities, and other statistics.

We are indebted to Mrs. Margaret Doran and the Medical Records Librarian Service in 51 hospitals and to the Registrars in other hospitals for the completion of our records and most particularly to the care and skill of the clinicians and laboratory workers in the performance of their routine work. We also are indebted to Mr. Howard Armstrong and the Visual Aids Staff for the excellence of the illustrations.

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# Infant Resuscitation

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APPROXIMATELY 6 per cent of the infants born at Sloane Hospital for Women in New York have severe respiratory depression at birth. To treat these babies successfully, everyone in the delivery room should be familiar with sound principles of resuscitation. "Everyone" includes the obstetrician, the anesthesiologist, the pediatrician, the medical students and the obstetric nurses, both graduate and undergraduate. The task of resuscitation should not be assigned to one of these persons or groups. The infant does not "belong" to the obstetrician, the pediatrician or the anesthesiologist. The most experienced available person should manage the severe depression promptly; nowhere is the success of teamwork more evident than in the delivery room.

### *1. Free Airway*

At the moment of birth, consideration is given to maintaining a free airway. The infant's head always should be lower than the trunk during delivery and until the pharynx has been examined and aspirated.[1] Gravity is a more important aid than any mechanical device. After prompt division of the cord between clamps, the infant, still in the head-down position, is placed in a bassinet with the head lowered. If the first inspiration consists of pharyngeal material rather than air, a strong basis is laid for development of secondary atelectasis, pneumonia and death in the first 48 hours. Mouth suction or electric suction (with a rubber catheter and trap) is used to empty the pharynx as long as any material remains in it. Prolonged suctioning is harmful both because of the marked bradycardia produced and because of removal of oxygen from the pharynx. After the pharynx is empty, almost all infants can be made to cough or sneeze (inspire deeply as well) by placing the end of the catheter just inside the nostril. After such a cough or sneeze the pharynx should be suctioned briefly again.

Amniotic fluid and its contents normally fill the tracheobronchial tree before birth, and al-

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

though the fluid is easily absorbed by the pulmonary circulation, and the foreign debris moved upward by ciliary action, the volume which the infant must handle is less if he can expel some by coughing.

Usually, infants do not require further attention. One group[7] believes that leaving the stomach empty has a favorable effect in preventing the later development of pulmonary complications, but we have not found such a relation as yet.

If artificial ventilation is necessary because of persistent apnea, it is essential to keep the tongue from acting as an obstruction in the pharynx. The tongue of a limp child lying on his back falls backward against the bodies of the cervical spine and obstructs the passage of air from either the nose or mouth. A small plastic pharyngeal airway placed between the tongue and palate corrects this obstruction immediately and always should be inserted if some type of positive pressure breathing is planned. If the infant has enough tone to keep his tongue forward in his mouth, he does not need the artificial ventilation.

When inflation of the lungs does not produce a slight rise of the upper chest, some obstruction still is present. One should rule out choanal atresia by slipping the catheter into the nasopharynx; this rare anomaly necessitates tracheostomy. More often the obstruction is at the larynx, and direct laryngoscopy is immediately indicated if efforts at ventilation do not improve the child's condition after two to three breaths. We have encountered both blood clots and vernix caseosa as the cause of obstruction, and these were removed easily by direct suctioning. If a complete laryngeal web is seen, immediate tracheostomy is indicated.

### *2. Ventilation*

The best ventilation is accomplished by the infant himself, and very few babies need any mechanical assistance. After making sure the pharynx is empty, a brisk slap on the soles of the feet will bring about sharp inspiration and precipitate crying. Obviously, a child deeply depressed and in shock is not so stimulated. If respirations are very inadequate or absent, some type of IPPB (intermittent positive pressure breathing) should be applied. Numerous mechanical devices are available for this purpose, or mouth-to-mouth inflation is always available and does not get out of order. The principle of application is a short, sharp "puff." Better results and less lung damage are produced by one or two such puffs than by a low pressure application of several seconds' duration.

The best gas to use is oxygen-enriched air. We know that excessive exposure to 100 per cent oxygen produces secondary atelectasis, pulmonary hemorrhage and retrolental fibroplasia in premature infants. It is doubtful whether a few seconds' use of 100 per cent oxygen in the delivery room will be followed by such complications, but this procedure will be discontinued when a practical method of applying positive pressure with a mixture of air and oxygen has been developed.

If application of positive pressure using a face mask does not bring improvement in two to three breaths, direct laryngoscopy and insertion of a flanged endotracheal tube are indicated. The flange prevents the tube from being inserted below the carina and allows a snug fit at the cords. The endotracheal route is the most efficient and direct in ventilating lungs, and the entire delivery room personnel should take all opportunities to practice intubation in warm, dead infants.

### *3. Position*

The head-down position from the moment of birth already has been stressed. There is much current discussion of the proper position of the infant in relation to the placenta before the cord is clamped. Since no competent valves function in the umbilical cord, blood volume easily can be shifted to the infant or to the placenta. In the case of a sensitized Rh infant it is recommended that the baby be held above the level of the placenta for 5 to 10 seconds before clamping the cord, thus lessening the likelihood of hypervolemia after exchange transfusion. We feel strongly that premature infants should *not* be held below the level of the placenta, for a large increase in blood volume will result. We believe

TABLE 1

EVALUATION OF THE NEWBORN INFANT; METHOD OF SCORING

| SIGN | 0 | 1 | 2 |
|---|---|---|---|
| Heart rate | Absent | Slow | Over 100 |
| Respiratory effort | Absent | Slow<br>Irregular | Good<br>Crying |
| Muscle tone | Limp | Some flexion of extremities | Active motion |
| Response to catheter in nostril (tested after oropharynx is clear) | No response | Grimace | Cough or sneeze |
| Color | Blue<br>Pale | Body pink<br>Extremities blue | Completely pink |

at present that this hypervolemia is related to the high incidence of hyaline membrane in premature infants. The best "routine" position is level with the placenta. The cord should be clamped promptly to allow immediate attention to the airway. After respiration is established, a head-up position will provide a larger thoracic cage for the expanding lungs, since the weight of the viscera lowers the diaphragm. At present, we feel this position is desirable.

### *4. Temperature*

The time-honored habit of keeping babies warm at all times is undergoing investigation. Cooler temperatures reduce tissue metabolism considerably, and warm ones raise it. Theoretically, cooling would be of aid to small, sick infants with respiratory insufficiency. There are few data regarding the normal behavior of the temperature after birth. The full-term infant's temperature drops 2 to 3° F., whereas the premature infant's may drop 4 to 8° F. and remain at that level for one or two weeks, apparently without detriment. A controlled experiment is under way at the Babies Hospital to study the survival of premature infants at different environmental temperatures. Our present practice is to omit hot water bottles, warmed blankets and other undue covering.

### *5. Humidity*

Controlled experiments do not provide evidence that excessive humidity or vaporization of various wetting agents improves survival in the newborn period.

### *6. Use of Drugs*

Rarely are agents other than oxygen indicated in the delivery room. If maternal depression exists, and if it is likely that it was caused by an opiate, intravenous injection of 0.25 mg. of *N*-allylnormorphine into the umbilical vein is worth a trial. If this is done and the diagnosis is in error, moderate sedation is produced in the infant.

Antibiotics always should be used after difficult resuscitation, and digitalis frequently is of help in severe cardiac problems.

### *7. Scoring*

Every infant is evaluated 60 seconds after birth according to a simple, objective scale, reproduced in table 1.

### *8. Gastric Aspiration*

After respiration is well established, every infant's stomach is aspirated by introducing a soft rubber catheter and aspirating the contents. The main purpose is to rule out esophageal atresia, the second purpose being to measure the gastric contents. If the tip of the catheter is not seen in the left half of the abdomen, a stethoscope is placed over the abdomen and a short puff of air is blown into the catheter. No noise indicates atresia.

### *9. Immediate Neonatal Diagnosis of Operable Anomalies*

I already have mentioned esophageal atresia. If more than 50 cc. is aspirated from the infant's stomach, the abdomen should be x-rayed

within the hour to rule out duodenal or jejunal atresia. Absence of gas below the pylorus indicates atresia and immediate operation.

The chest should be auscultated in the first few minutes. A shift in loudest cardiac sounds and absent breath sounds in one side of the chest suggest diaphragmatic hernia, another operable emergency.

Imperforate anus should be treated by operation immediately. The newborn infant is most resistant to surgical assault and anesthesia in the first 24 hours after birth. Every delay in diagnosis of an operable anomaly jeopardizes his chances for survival.

### *10. Maternal Polyhydramnion*

A history of maternal polyhydramnion should lead to an especially thorough search for anomalies, most of which are operable. We have found the following anomalies to be directly associated with polyhydramnion: anencephalia, hydrocephalus, tracheo-esophageal fistula with esophageal atresia, diaphragmatic hernia, congenital cardiac disease, duodenal and upper jejunal atresia, volvulus, and perforated stomach. Rapid diagnosis in the delivery room is one of the most hopeful means of reducing neonatal mortality.

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# The Relationship of Upper Respiratory Infections to Congestive Heart-failure in Patients With Heart Disease

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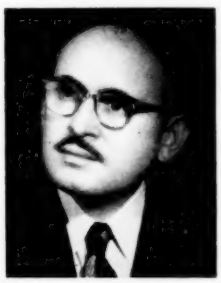
INFECTIONS, particularly of the upper respiratory tract, are frequent precipitating causes of congestive heart-failure in patients with heart disease.[1-7] However, these infections are not as commonly recognized as precipitating factors as are overexertion, arrhythmias, hemorrhage, anemias, electrolyte imbalance, coronary artery disease and the direct cardiac-damaging infections, such as rheumatic fever. Because of this lack of recognition, many instances of cardiac failure occur which could possibly have been avoided or halted early.

SAMUEL WALDMAN



LOUIS PELNER

It is customary to practice prophylaxis in patients with chronic rheumatic or congenital heart disease to prevent subacute bacterial endocarditis.[8,9] Antibiotics or chemotherapeutic agents are regularly administered before, during and after a tooth extraction, tonsillectomy or other surgical procedure which is likely to create temporary bacteremia.[9,10] Similar treatment applied to all patients with chronic heart disease who develop respiratory infections would help prevent heart-failure.

It has been well stated by Grant that "once the heart has adjusted to a constant load, no further deterioration occurs until another load is added."[11] Cardiac failure rarely results from progressive hypertrophy and dilatation alone.[5] We feel that the severe cough, tachycardia and fever of a respiratory infection, and the resulting derangement caused by these symptoms,

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may be sufficient to act as the additional load or stress which results in cardiac decompensation in a patient with a limited cardiac reserve.

### *Case Reports*

Case reports illustrating the relationship between various respiratory infections and heart-failure are presented. Combined therapy in these cases achieved excellent results. Many of these patients served as their own controls, having been treated for heart disease for several years with and without failure and with and without infections. Fever and severe cough were common to all these cases of respiratory infections.

*Case 1*—Left ventricular failure prevented by prompt treatment of a respiratory infection.

A 63 year old white man had been treated since 1944 for arteriosclerotic heart disease with auricular fibrillation. The auricular fibrillation, originally of the paroxysmal type, became persistent in 1951. Digitalis was administered continuously to keep the ventricular rate between 70 and 80 per minute. The patient began to have repeated episodes of left ventricular failure when the arrhythmia first became fixed. These attacks were then prevented by digitalis, plus an occasional injection of a mercurial. Maintenance doses of digitalis were continued.

In January 1952, the patient had an acute subendocardial infarction which again precipitated attacks of nocturnal dyspnea. When he recovered from the infarct, the attacks progressively decreased in frequency and then stopped. In January 1954, following an upper respiratory infection with fever, sore throat and severe cough, attacks of nocturnal dyspnea with "sizzling in the chest" recurred. The patient treated himself with aspirin, but attacks continued almost nightly, despite the regimen of digitalis and low salt diet. Cultures of throat scrapings were reported as showing streptococci. The DECHOLIN® circulation time was 34 seconds (arm to tongue). Penicillin was administered parenterally in doses of 600,000 units daily. The respiratory infection subsided within three days. No mercurials were given, but the digitalis was continued, and no further attacks of paroxysmal dyspnea occurred. The circulation time one week later was 18 seconds.

In September 1954 a similar episode with fever and cough was treated with penicillin, after the first attack of paroxysmal dyspnea wakened the patient. No further attacks occurred thereafter.

*Case 2*—Failure of prophylactic cardiac therapy to prevent the onset of decompensation in the presence of infection. Restoration of compensation was prompt after the addition of antibiotic therapy.

A 68 year old white woman had been treated since 1944 for arteriosclerotic heart disease with coronary insufficiency and anginal syndrome. Her chronic illness was punctuated in 1949 by pulmonary infarction secondary to phlebothrombosis in the right leg.

In March 1954 the patient was hospitalized with primary atypical pneumonia; recovery was uneventful. No digitalis or mercurials were required.

In May 1954 increasing symptoms of coronary insufficiency developed with evidence of left ventricular heart-failure. Treatment with digitalis, mercurials and nitroglycerin was effective in relieving the patient's symptoms. Digitalis administration was maintained and an occasional injection of a mercurial was necessary. In October 1954, the patient developed an acute streptococcal pharyngitis and bronchitis with temperature of 102.4° F. The cough was severe and dyspnea increased. Rales were audible at both bases and slight peripheral edema was noted. The patient was taking digitalis, and she had been receiving mercurials parenterally every two to three weeks. Penicillin was administered at once and antitussive agents were given. In five days the dyspnea had subsided, the cough had disappeared and the patient again was restored to comfortable compensation. No increases in digitalis dosage or mercurial administration were made during this time.

*Case 3*—Congestive heart-failure controlled rapidly by treatment of upper respiratory infection accompanied by severe cough.

A 36 year old Negro woman had been under our care since 1951 for rheumatic heart disease with mitral and aortic insufficiency and

stenosis. Auricular fibrillation was persistent. The patient was receiving maintenance doses of digitalis, and she had an apical ventricular rate of between 66 and 78 per minute. Hepatic enlargement, 3 cm. below the costal margin, was present when she was first seen. Dyspnea on exertion was mild, and there was no peripheral edema.

In September 1954 she developed an acute pharyngitis and bronchitis with a hacking, severe cough. Symptomatic therapy, plus tetracycline, effected some improvement which gave the patient a false sense of security, so that she discontinued treatment as soon as she felt comfortable. One week later, however, the bronchitis recurred, her temperature mounted to 102° F., and the apical heart rate was approximately 118 per minute. Bilateral basal rales were present. There was venous congestion in the neck and the Decholin circulation time was 38 seconds. Cough was incessant and accompanied by hemoptysis. Tetracycline was administered again in a dose of 0.5 gm. every six hours. The dose of digitoxin was increased from 0.1 mg. to 0.2 mg. daily and 2 cc. of a mercurial was injected intramuscularly. In 24 hours the patient's temperature was normal; in 48 hours she coughed only occasionally, and the basal rales had disappeared. Blood-tinged sputum continued for two days. The ventricular rate declined to 76 per minute. Digitoxin was again reduced to 0.1 mg. daily and the patient again regained her previous state of relative compensation.

*Case 4*—Congestive heart-failure controlled readily by supplementing conventional treatment with treatment of the respiratory infection. Subsequently, similar episodes were prevented.

A 45 year old man, a dentist, has had hypertension since 1951. He had previously had many attacks of acute bronchitis, with marked wheezing, following upper respiratory infections. Blood pressures taken at various times before 1951 were always within normal limits. Ephedrine and other adrenergic drugs given for symptomatic relief had no lasting effect on the blood pressure.

On June 2, 1951, during a routine physical examination, his blood pressure was noted to be 200/100. He was treated with the drugs then available, such as aminophylline, inositol hexanitrate, and phenobarbital, without effect on his blood pressure, which was stabilized at around 220/110. He had no headaches and continued to work without discomfort.

On August 3, 1952 an upper respiratory infection with acute bronchitis developed, accompanied by marked wheezing and coughing. Simple medications were given, but severe dyspnea occurred within 24 hours. He was given penicillin and a mercurial diuretic by injection, and the dyspnea slowly subsided.

On March 22, 1953 there again developed an acute bronchitis with severe cough and wheezing. The patient's blood pressure was 240/140 and his heart was enlarged. During the night, following a severe coughing bout, he had a severe dyspneic paroxysm which required a mercurial diuretic and rapid digitalization. The dyspnea subsided, but within four days he required a mercurial diuretic.

The optic disks were normal, but there was diffuse narrowing and increased tortuosity of the arterioles. Arteriovenous nicking was present (grade II). The electrocardiogram, previously normal, showed marked left heart strain and digitalis effect. Physical and x-ray examinations disclosed enlargement of the heart and basal congestion of the lung fields. The phenolsulfonphthalein excretion test and the blood chemical findings were normal.

A first stage lumbodorsal splanchnicectomy was carried out on April 27, 1953 and a second stage was done on May 11, 1953. The patient was given digitoxin throughout his hospital stay and was able to leave the hospital on May 25, 1953.

Following the operation his blood pressure ranged from 130/110 to 150/90 and he had no symptoms referable to his heart or blood pressure.

On January 14, 1954 an acute bronchitis with severe cough, fever and wheezing developed. He was given a sedative cough mixture and one dose of penicillin (600,000 units) intramuscularly. The cough did not improve and within 24 hours he was again in myocardial failure. The digitalis dosage was increased and he was given one DIAMOX® tablet

daily. Because of the slow response and continued dyspnea, it was felt that his respiratory infection was an important factor in producing the state of failure. Tetracycline, 1 gm. daily, and aminophylline by injection and suppository were given. Under this regimen, he recovered from the myocardial failure in two weeks. During the acute period, he could not walk 50 steps without severe dyspnea. Plans were made to reduce his working hours.

Following recovery from the upper respiratory infection, the cardiac compensation improved and he was able to discontinue taking Diamox, but he continued the maintenance dose of digitalis. Reserpine and Veratrum drugs were administered, with a resulting blood pressure range between 170/100 and 160/100. He now does a full day's work and walks to work from his home, a distance of about eight blocks.

On September 27, 1954 bronchitis occurred. This time prompt administration of tetracycline, 1 gm. daily, prevented any myocardial failure. He was given a supply of the antibiotic to be taken at the start of any upper respiratory infection. He had one additional episode of upper respiratory infection which responded rapidly to treatment, and failure did not ensue.

*Case 5*—Congestive heart-failure controlled by supporting conventional therapy with treatment of the precipitating infection.

A 58 year old white woman, a hospital clerk, presented a history of hypertension for which she had been treated with digitalis and mercurials during the past year. Examination showed no evidence of myocardial failure; the heart was not enlarged; the venous pressure was normal; the Decholin circulation time was within normal limits, and the electrocardiogram was normal. Digitalis and mercurials were therefore discontinued and she did well. Her blood pressure was maintained at around 160/100.

An upper respiratory infection with severe cough and slight fever (100.6° F. rectally) developed. Initial treatment consisted of an antihistaminic cough mixture, aspirin and bed rest. About 36 hours later she became extremely dyspneic and was hospitalized. Both percussion and x-ray examination showed her heart to be enlarged. There were crepitant rales at the bases, and an x-ray showed basal congestion. Her blood pressure fell to 130/100. She required oxygen therapy, rapid digitalization and injection of a mercurial. Response to therapy was slow until three days later, when it was realized that the infection was still a potent factor in maintaining the state of failure. Chlortetracycline, 1 gm. daily in divided doses, was then given. It required about two weeks for compensation to be completely restored.

Following her discharge from the hospital, she was able to return to work and once again showed no evidence of heart-failure. Again her venous pressure and circulation time were normal.

*Case 6*—Repeated respiratory infections in a patient with arteriosclerotic heart disease and bronchiectasis caused heart-failure, subsequently controlled and prevented by concurrent administration of antibiotics.

A 72 year old white man, a cabinetmaker, was known to have arteriosclerotic heart disease complicated by bronchiectasis. Occasional acute bronchial infections had required treatment since 1944. In 1947 a severe attack of bronchitis responded promptly to penicillin administered by aerosol and intramuscularly. There was constant evidence of bronchiectasis with harsh, coarse rales and occasional large bubbling rales at both pulmonary bases. In 1952 the patient had bronchopneumonia with fever and severe harassing cough. He responded to penicillin and sulfonamide drugs within seven days. The pulmonary situation returned to its former status. Chest x-rays at this time showed a slightly enlarged left ventricle, some pulmonary fibrosis, dilated basal bronchial shadows and emphysema with blebs in the right upper lobe.

In November 1953 a respiratory infection with fever and bronchitis again occurred. This time it became evident that congestive heart-failure was a factor in the patient's symptomatology. The dyspnea exceeded that of any previous episode. Palpitation and tachycardia were prominent. Cough became persistent, resistant and much accentuated on reclining.

Bloody sputum was expectorated. Slight leg and ankle edema became evident. A Decholin circulation time test (arm to tongue) was 32 seconds. The patient was digitalized and mercurials were administered in addition to daily injections of penicillin. Antitussive agents were given. Again progressive improvement was noted and the patient recovered in two weeks. Thereafter, he was maintained on digitalis with supplements of Diamox.

In March 1954 a respiratory infection with fever and severe cough caused a marked increase in dyspnea, some ankle edema and substernal distress. The patient was put to bed and given an increased dosage of digitalis and a mercurial injection. Potassium iodide and cough sedatives were also given during a control period of four days. Improvement was slight. Sputum studies at this time revealed a mixed infection with staphylococci, streptococci, no tubercle bacilli, many white blood cells, occasional red blood cells, and many elastic fibers. Tetracycline was then administered, 0.5 gm. every six hours. Four days later improvement was manifest with relief of cough and dyspnea. Fever subsided in 48 hours. The circulation time was reduced to 18 seconds two days later.

In October 1954, while the patient was still receiving maintenance doses of digitalis and Diamox (the latter 250 mg. daily for five days per week), he reported the onset of another respiratory infection. This time tetracycline was given at once, 250 mg. every six hours. The cough and dyspnea increased slightly, diffuse rhonchi were audible, but there was no fever and no further evidence of failure. The patient is now on a prophylactic regimen taking 250 mg. of tetracycline twice daily.

### *Discussion*

It is customary to classify cardiac patients according to the nomenclature established by the criterion committee of the New York Heart Association.[12] This includes etiology, anatomic and physiologic diagnoses, functional capacity and therapeutic classification. Concomitant disorders are ordinarily affixed to the cardiac diagnosis as accompanying conditions. However, in considering the problem of congestive heart-failure, it appears that these disorders may be the precipitating factors. Since these factors include all causes capable of creating cardiac overload, it is imperative that such conditions be sought, recorded and treated in every case of heart-failure.

We feel that one of the most important precipitating causes of heart-failure, besides the underlying heart disease itself, is severe respiratory infection. Some mechanism causes failure in a heart which, though diseased, has been compensated for a long time. When an additional load or stress is applied, the heart becomes decompensated. One of the most common stress factors is severe upper respiratory infection. Every book on cardiology mentions this fact, but no special attention is given to it in considering the prevention and treatment of the cardiac decompensation.

Respiratory infections probably provoke the development of congestive heart-failure by several pathophysiologic alterations. Excluding rheumatic fever sequelae and their associated cardiac complications, or subsequent subacute bacterial endocarditis, many other factors contribute to the development of failure in patients with heart disease. Cough is an intense straining effort involving extensive muscular exertion and acts as a severe stress agent on the heart.[13,14] A recent electrocardiographic study of children with pertussis revealed the almost constant presence of electrocardiographic changes consistent with right heart strain during the period of the most severe coughing paroxysms.[15] The electrocardiograms returned to normal in all instances with recovery from infection and decrease of cough. The tachycardia associated with cough and fever, and the fever itself, place increased demands on the heart, both physically and metabolically.[16-18] For each degree rise of temperature above 37° C., oxygen consumption increases about 13 per cent. As a result of increase in heart rate and stroke volume, cardiac output is increased. Cardiac work is thus increased and this augmented load may cause the heart to fail.[17]

Despite its value in increasing cardiac output, tachycardia with diastolic shortening may contribute to impaired cardiac functioning,

especially in the presence of coronary artery disease, or when the rate is very rapid (over 130 per minute). By decreasing cardiac output, the tachycardia compromises cardiac function.[16,17] Many respiratory infections, including viral diseases, have caused alterations in the electrocardiograms of apparently normal hearts—especially affecting the S-T and T waves—indicating some effect on the myocardium, which is probably due to toxic, metabolic or electrolytic changes or to interference with mechanical efficiency.[19-21] These alterations are not detectable clinically, but obviously indicate some myocardial alteration, even though temporary. Functional changes may cause electrocardiographic changes and occur without histologic changes, while histologic changes may exist with or without electrocardiographic changes.

Some infections cause a decrease in urine output probably due to an increase in the antidiuretic hormone.[22] It is interesting to note that it has been demonstrated experimentally that an increase in cerebral venous pressure by neck compression causes a rise in excretion of antidiuretic hormone.[23] Since coughing increases the venous pressure by increasing the intrathoracic pressure, this may also contribute to an increase in antidiuretic hormone. In addition, it has been shown that neck compression under the same conditions which cause a significant increase in sodium excretion in normal subjects failed to do similarly in patients with congestive heart-failure.[24] Altered electrolyte balance may result from increased adrenocortical activity during the acute stages of infection.[1,22] Bronchial congestion may further increase pulmonary hypertension and stasis, especially in patients who have impediments to blood flow into the left side of the heart. Restlessness, insomnia and the increased ventilatory demand created by respiratory infections also augment the load on the myocardium.

How upper respiratory infections may affect the cardiovascular system by disturbing salt and water metabolism and induce failure was the subject of recent investigation.[25] The subjects used were normal medical students without evidence of heart disease. No changes in salt and water metabolism were noted during upper respiratory infections. There were also no changes in the levels of hemoglobin, erythrocytes, hematocrit, urine electrolytes, Evans blue space, and thiocyanate space and body weight. However, in patients with heart disease with varying degrees of diminished myocardial reserve, results might have been different.

One of the factors not discussed in this report is the incessant cough associated with a severe respiratory infection. If this symptom could be evaluated in patients with limited cardiac reserve, we feel that it would prove to be an important factor in causing cardiac decompensation.

Respiratory infections were found to be the commonest exciting cause of heart-failure in patients who had previously undergone mitral commissurotomy.[26]

It thus becomes extremely important and fundamental to determine the precipitating causes of heart-failure as well as the underlying causes of the heart disease itself. These are the potentially tangible factors which can be reduced or eradicated more easily in the patient who already has heart disease. Careful management of these patients, with special regard for prevention or early control of the respiratory infection, may prevent, abort or postpone the onset of congestive heart-failure and possibly add to the life span of the individual by decreasing the number of failure episodes. The more frequently a patient has acute heart-failure, the more extensive is the encroachment on reserve power, the greater the possibility of increasing dilatation and hypertrophy and the worse the prognosis.[27] This is especially true in instances of left ventricular failure. Attention directed to etiologic prevention of further invasion of the myocardial reserve is thus indicated.

Sodeman and Burch[27] showed that in 57 patients with a known precipitating cause of heart-failure, treatment rapidly restored compensation in 40, 14 failed to compensate to the extent of engaging in usual activities, and three could not be followed. Of 47 patients with a gradual onset of failure without an apparent immediate cause, 46 were unable to

regain a comfortable state of compensation (refractory).

Whenever congestive heart-failure develops, it is incumbent on the physician to seek its cause, since properly directed therapeutic efforts become more effective. Uncontrollable precipitating factors of failure are unfavorable prognostic omens.[2] The presence of infection causes increased resistance to conventional therapy for decompensation. Patients treated early usually recover more readily from the respiratory infection and the incipient heart-failure if it has appeared.[27] The response is then usually satisfactory and prompt, and prolonged cardiac therapy may not be required. When treatment is aimed only at the cardiac failure, the response may be poor and the disease may be considered intractable. If the provoking factor is treated and eliminated, digitalis, diuretics and dietetic restrictions may not be required permanently, although they are necessary during the acute phase.

Only recently it has been demonstrated that in patients with chronic pulmonary diseases, the first signs of decompensation followed an episode of acute bronchitis.[28] Arterial gas studies showed acute anoxia to be present in these patients. In one instance, there was a complete disappearance of signs of congestive heart-failure in 24 hours with no specific treatment directed toward the failure. Treatment included oxygen, artificial respiration, bronchodilators and antibiotics.

When the symptoms of congestive heart-failure subside rapidly under proper treatment, the prognosis is better. The more rapid the response and the less prolonged the treatment required, the better is the patient's outlook for immediate and continued recovery.

McVay and his associates[3,4] have suggested the prophylactic administration of chlortetracycline to prevent respiratory infection in patients already in congestive heart-failure where increased susceptibility to infection exists. They noted a definite diminution in the incidence of upper respiratory infections, bronchitis and pneumonias. Indeed, they found improvement in appetite, strength and sense of well-being. We feel that such therapy, either prophylactic or therapeutic, need not be pursued only in the presence of heart-failure but before the advent of heart-failure, where possible, in patients with chronic heart disease.

Once a respiratory infection is apparent, its relation to the heart status must be evaluated. Upper respiratory infections may be mild and, with or without treatment or medical care, subside readily with no aftermath and without precipitating failure. However, the infection and its accompanying manifestations may induce failure. Here the therapeutic attack is two-dimensional, and if the respiratory condition was the precipitating cause of failure, a rapid response to therapy may be anticipated. If the respiratory infection is overlooked, therapy may be futile or unduly prolonged.

The presence of a respiratory infection, particularly bronchitis, may make difficult the evaluation of the presence or absence of failure. If both are present, it may be difficult to define the predominating disorder. The differential diagnosis involves answers to such questions as: Is it simple bronchitis? Is there failure? Are both present? Did the infection induce the failure? Is the failure simulating bronchitis? The differentiations involve careful history-taking and the disclosure of other manifestations of congestive failure, such as evidence of increased venous pressure, hepatomegaly, peripheral edema and increased circulation time. A test dose of a mercurial not infrequently helps solve the diagnostic dilemma by producing diuresis with increased comfort in patients with failure. Although fever frequently occurs in failure, it is more apt to be present and reach higher levels in respiratory infections. The chest findings in bronchial conditions are usually more disseminated than in failure where the bases are usually involved, except in advanced left ventricular failure where similar findings may be noted.

When a patient with known heart disease becomes ill with an upper respiratory infection, we advise immediate treatment. Bed rest, aspirin and antitussive agents such as codeine, HYCODAN® bitartrate (dihydrocodeinone) or DOLOPHINE® (methadon hydrochloride) are prescribed in sufficient amounts to be effective. Nasal decongestants and antihistamines, bronchodilators and expectorants and oxygen

are given as indicated. Antibiotics, of which we use penicillin and the various tetracyclines, are given if there is fever, pharyngitis and bronchitis. If signs of congestive heart-failure supervene, this treatment is continued while specific therapy for the failure is inaugurated, or augmented if such therapy has been given on a maintenance basis.

### *Summary*

Cases are reported to show that respiratory infections can precipitate congestive heart-failure in patients with heart disease. The possible mechanisms by which such complications are brought about are discussed. The common denominators in these cases were cough and fever.

Antibiotic therapy promptly employed, in addition to the conventional therapy for congestive heart-failure, usually will prevent or abort heart-failure, or rapidly restore the patient to the previous state of compensation. Less cardiac therapy, administered for a shorter period, may thus be required.

Prophylactic administration of antibiotics to patients with heart disease not in failure may be used to prevent the onset of failure due to intercurrent respiratory infections.

Patients and physicians alike should be alerted to the preventive aspects of congestive heart-failure.

Reports of cases 7 to 10 will be included in the authors' reprints.

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DIAGNOSTIC CLINIC

# Carcinoma of the Thyroid

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ALTHOUGH carcinoma of the thyroid is relatively rare in general practice, it becomes a very important problem when it occurs in a member of your own family or when you do see it in a patient, because of its serious complications. Its incidence probably is increasing; certainly it is increasing among younger persons, and it always has been fairly common in persons of advanced age.

The important thing relative to carcinoma of the thyroid is not its active treatment but its recognition in a premalignant stage. In approximately one-third of all thyroid malignancies, irrespective of the treatment given, only palliative benefit can be accomplished, whereas in the early or premalignant stage one can, of course, anticipate providing complete relief.

The tragedy of the problem of thyroid carcinoma lies in the fact that clinically we cannot make a positive diagnosis in a large proportion of cases, and in the absence of symptoms active treatment may not be recommended. In fact, in cases of histologically proved carcinoma of the thyroid, review of the clinical records reveals that in approximately half the cases malignancy was not suspected.

There are obvious signs of thyroid malignancy which we are on the lookout for when the thyroid gland is enlarged. One is nodularity of the gland with localized hard areas, particularly in a patient who has not had previous enlargement of the thyroid. A change that is almost certain to indicate malignancy or is due to diffuse inflammatory disease or thyroiditis is fixation of the gland, causing it to move with difficulty on deglutition; under

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these circumstances the lesion is likely to carry an unfavorable prognosis. Involvement of the lateral cervical nodes with or without fixation indicates a lesion of this type. Hoarseness, which may occur equally with an inflammatory condition or thyroiditis, usually denotes a fairly advanced stage if the lesion is malignant. Then when we think of difficulty in breathing, choking, or difficulty in swallowing, we know that we are dealing with a serious problem.

The many different forms of thyroid malignancy must be considered separately, and certainly in interpreting results it is important that we realize the type of lesion with which we are dealing. Some of these forms, although actually not classifiable as thyroid malignancies, properly must be considered in discussing carcinoma of the thyroid.

The first is a nodule removed from the gland which on histologic section shows only blood vessel invasion within the confines of the tumor or adenoma; this was described by Allen Graham in 1924. A few of these show evidence of distant metastases, but on the whole the results of their removal are quite satisfactory.

Next in the group of localized tumors is a papillary cystadenoma, usually found in a long-standing nodule. There may be only slight invasion of the capsule or histologic evidence of carcinoma within the substance of the nodule, without any spread beyond this.

A third form that is not a serious type is carcinoma *in situ* or sclerosing or noninvasive carcinoma. This lesion can be recognized at operation as a small white or gray spot, perhaps with a surrounding area of extension. Local removal by hemithyroidectomy, with confirmation by pathologic section, is all that is required for its relief. It is not a true carcinoma and should not be included with the other carcinomas which we will consider.

The commonest malignant tumor of the thyroid is the papillary type of tumor which tends to spread to the regional lymph nodes. It usually occurs unilaterally but is bilateral in about 10 per cent of cases.

The next form is more malignant, an adenocarcinoma or alveolar carcinoma, usually metastasizing through the lymphatic system but also by venous extension.

The third group of serious thyroid cancers is carcinoma simplex, encompassing a whole group of histologic types—the small cell carcinoma, the giant cell carcinoma and those lesions sometimes considered as sarcomatous.

Through the courtesy of Dr. Forrester Raine of the Veterans Hospital in Milwaukee, we have here two patients representing different problems concerned with thyroid cancer.

The first is a 64 year old man who entered the hospital with a history of a lump in his neck of many years' duration; the history gives it as 13 years, but the patient tells me he has had it 40 years or more. He complains of a feeling of pressure in his neck and some difficulty in swallowing and wearing a tight collar. He has also described a choking sensation when he elevates his arms or lifts things.

I will demonstrate a very useful method of examining the thyroid to determine whether a nodule is discrete or whether the gland is diffusely changed. This man, by the way, has been in military service for a number of different "hitches," and at one time he was advised to carry this nodule with him to the grave—which is, of course, poor advice.

With his chin elevated, there is no obvious enlargement in his neck, and yet he himself discovered a nodule and noted its continuing presence over a period of years. A hard nodule is present. Because of the fixation of the thyroid gland to the larynx by the superior thyroid vessels entering it, the thyroid is suspended in this position and can be palpated readily, as taught by Dr. Lahey. The patient swallows while the examiner places his fingers behind the sternocleidomastoid muscle and the thumb in front so that the entire lobe can be palpated and run through the fingers as the gland rises. The left lobe of his thyroid is normal. By turning his chin to the side, releasing the sternocleidomastoid muscle, I can get my fingers in behind it and palpate the gland as he swallows. He has a large, hard nodule on the right side which goes below his clavicle. A roentgenogram reveals some deviation of the trachea to the left side.

What treatment should one advise in this

case? During a recent examination at the hospital in which full studies were done, operation was advised. He does not exhibit evidence of abnormal thyroid function. He should be operated on, and he is willing to accept this advice.

Under these circumstances the surgeon must obtain wide exposure of the entire right lobe and be able to palpate the left lobe carefully. He should immediately search for signs of adherence or invasion of the muscle, because in many such cases a malignancy can be recognized. If these signs are not present, a subtotal hemithyroidectomy, removing all of the nodule from the right lobe, is all that is required. If the facilities and an experienced pathologist are available, we think it is advantageous to do an immediate frozen section. Dr. Shields Warren and Dr. William A. Meissner, who do our pathologic studies at the Lahey Clinic and who have had large experience with these cases, feel quite confident that in most instances the presence or absence of malignancy can thus be determined.

However, if signs of malignancy are found at operation, a total lobectomy should be performed with removal of all of the right lobe, adequately visualizing the recurrent laryngeal nerve and parathyroids for their protection. Then, if facilities for frozen section are not available, one can determine what should be done subsequently without having to deal further with the thyroid on that side. The surgeon who takes this attitude is not embarrassed four or five days later when the pathologic report of carcinoma of the thyroid is returned, for which further operation is required. At our clinic, if a diagnosis of carcinoma were made from this frozen section, we would, depending on the type of malignancy, continue the operative procedure and do a neck dissection on the same side as the thyroid tumor.

The second patient is 60 years of age and has quite a complicated story. He is aware of the various possibilities relative to his lesion. This man had had a thyroid enlargement for 12 years without treatment when obstructive symptoms developed in July 1952. Subtotal thyroidectomy was done. It is not recorded whether or not carcinoma was recognized at the time of operation. The tissue removed was subsequently reported as adenocarcinoma of the thyroid.

A radioactive iodine tracer study was carried out. Some of the radioactive iodine was absorbed. He was given a dosage of 25 millicuries of $I^{131}$. Later that year he had another tracer study, but further uptake by the thyroid was noted and he received a second dosage. Two years later, pain developed in his hip and also in his ribs and back. Radioactive studies at that time showed evidence of metastases in these locations.

Roentgenograms revealed a moth-eaten appearance of the right side of the pelvis involving the head of the acetabulum, and nodules in the rib cage on each side. The trachea is considerably displaced to the right.

We are now confronted with planning further treatment. Of course, the important point in this man's clinical history is the period of almost 12 years when a relatively simple operation would have provided relief. He now has had 170 millicuries of radioactive iodine, with some relief of symptoms but little change in the metastases. As a result of that therapy, a hypoplastic anemia has developed, with pancytopenia, requiring multiple transfusions. However, he has been able to work part of the time; he last worked in February 1955.

He has some difficulty in walking, due partly to nerve involvement in the pelvis as well as to actual bone involvement. In addition, his right knee gives him some trouble, which probably is unrelated to the neoplasm.

What can we do for this patient at present? His condition has improved over the three year period of treatment. He has a large mass in the left side of his neck which, of course, is fixed and difficult to remove. A further operative procedure has been considered for removal of the malignancy in his neck, followed by a period of thyroid medication and further treatment with radioactive iodine.

Based on our experience with this type of cancer, I believe it would have been advantageous if a total thyroidectomy had been done originally, followed by deep roentgen therapy to the upper mediastinum and neck and then to the distant metastases. Reported

experience with radioactive iodine in treatment of thyroid metastases indicates that some benefit has been obtained but that cure cannot be anticipated. Radiation therapy of some type offers the only palliative benefit.

The actual incidence of carcinoma of the thyroid cannot be determined, and I must admit that the figures given below represent a selected group of cases from a busy thyroid clinic.

In a period of two years, 1,479 patients were operated on for thyroid disease at the Lahey Clinic. Of these, 78 had carcinoma of the thyroid—an incidence of 5.3 per cent. Only 104 cases involved nontoxic discrete fetal adenomas. Contrary to the usual belief, a discrete fetal adenoma is not a common finding. Its diagnosis is extremely difficult particularly in the Great Lakes region where diffuse nodular goiter is common. Rienhoff and Thomas reported a number of years ago that 12 per cent of patients with diffuse nodular goiter also have discrete fetal adenoma, and in our experience 8 per cent of patients with Graves's disease or primary hyperthyroidism similarly have a coincidental adenoma. Cases of diffuse nodular goiters numbered 644, primary hyperthyroidism or exophthalmic goiter 447, thyroiditis 93, and carcinoma 78.

Published reports of the relation of diffuse nodular goiter to malignancy carry a wide discrepancy as to the incidence of malignancy, varying from 1 per cent to approximately 30 per cent. The incidence in a group of 861 patients with nodular goiter in our series was 9.1 per cent; this group included all cases of nodular goiter, and if we included only the diffuse nodular goiters the figure would be considerably lower.

There is much controversy regarding the incidence of malignancy in discrete thyroid nodules. In our series a total of 104 discrete nodules was found, and 52 additional ones were seen in which the thyroid malignancy could be shown to arise from a nodule. Thus, in 52 out of 78 cases of thyroid carcinoma—about 65 per cent—the malignancy could be shown to arise in an adenoma.

If just these 156 cases were included, we would find that approximately one-third of the discrete thyroid nodules contained malignant lesions. We must recognize this as a selective group, since a number of these patients with discrete nodules had signs suggesting malignancy which led to their referral, but the high incidence certainly supports the position that all discrete nodules should be removed.

Our figures bear out Pemberton's findings that at least 33 per cent of nodules of the thyroid in young adults or in children are malignant. Five of our patients were less than 20 years of age, and five between 20 and 30; only a little more than half were more than 45 years of age, the group where one would expect a higher incidence of malignancy.

Thyroid nodules in adults who have not had previous enlargement of the thyroid will be malignant in nearly as high a percentage as in the young group. The important point is that so often the young adult or the family of a child is advised that a small nodule need not be removed unless it produces symptoms. That is a very serious stand to take, because malignancy will be overlooked in too high a proportion of cases. This was well illustrated recently by the case of a young girl who was ready to return to school when her mother insisted on an examination and the family physician found a small nodule under the sternocleidomastoid muscle. He recognized it for what it was, even though nothing could be felt in the right lobe of the thyroid. The nodule was removed and proved to be papillary adenocarcinoma. A neck dissection was done and a tiny primary lesion was found in the homolateral lobe, even though nothing could be felt.

The only sign of malignancy in 58 of our 78 cases of thyroid carcinoma was a pre-existing goiter. In two, a node was felt in the lateral neck. Six patients had had a previous biopsy. Nine patients had no symptoms whatever; the nodule had not been noticed and was discovered on routine examination.

Symptoms had been present for five years in 25 cases, slightly less than a third. We have found that those patients with symptoms of short duration in whom a pre-existing goiter is not noted are likely to have cancer.

Our preoperative diagnosis is quite accu-

rate for most types of thyroid disease, but this is not true of the diagnosis of malignancy. Thirty-seven of these patients had a diagnosis of discrete fetal adenoma, and in only 15 was there a clinical note that this was an adenoma, but it had certain clinical signs of possible malignancy. In one of these the diagnosis was cervical adenitis. Ten patients had a diagnosis of diffuse nodular goiter. One had diffuse nodular goiter suspected of carcinoma, one had thyroiditis, and only 11 had an outright diagnosis of malignancy. The latter lesions were the infiltrating, fixed type.

A preponderance of papillary tumors was encountered. No one knows today why papillary tumors are increasing in incidence, but I think this is noted in all the reported series. The carcinoma simplex group included 18 patients—and this is the group I referred to previously in which all that can be done is to offer palliative relief by combined surgical and radiation treatment.

An aggressive surgical approach is necessary in order to deal satisfactorily with carcinoma of the thyroid. If a unilateral lesion is of either the papillary or the alveolar type, whether or not the lymph nodes are palpable in the neck, a homolateral radical neck dissection should be done. In our series, this was done in 26 instances of papillary tumors, and in exactly half, nodes were involved. This is irrespective of whether or not the nodes could be felt.

At the 1955 meeting of the American College of Surgeons in Chicago, Dr. Frazell reported a 61 per cent involvement of the cervical lymph nodes in papillary tumors of the thyroid when clinical examination failed to reveal lymph node enlargement. In an earlier series of 52 cases which I reported in 1948, lateral node involvement was present in 87 per cent of those in which radical neck dissection was carried out. I think the same principles apply in surgical management of carcinoma of the thyroid involving one lobe as in surgical management of carcinoma of the breast whether or not nodes are felt in the axilla.

For papillary and alveolar tumors, we do total lobectomy, removing the prethyroid muscles, sternocleidomastoid muscle, internal jugular vein and deep cervical lymph nodes. One may hesitate to advise this for younger individuals, and yet these are the patients who have the best chance for cure. We believe this type of procedure should be employed, eradicating all possibility of malignancy at least in the neck.

The disease is bilateral in more than 10 per cent of cases. Sometimes the bilateral involvement is found only after operation and probably is either recurrent from the opposite side or of multicentric origin. In doing a bilateral neck dissection, we believe it advisable to leave the jugular on the second side. Otherwise, marked swelling of the face and scalp may result. It may require six weeks for all signs of the venous congestion to disappear.

The scar resulting from this type of operation for carcinoma of the thyroid is not an unsightly one, even though it is long; it extends obliquely from the mastoid process to the sternoclavicular joint.

When this procedure has been carried out and pathologic section has proved that lateral nodes in the neck are involved, we then advise deep roentgen therapy. For the more favorable cases, which represent about 66 per cent, this combined treatment carries a high five year survival rate.

Palliative benefit may be provided in advanced thyroid malignancy by thyroidectomy and postoperative roentgen therapy, but cure cannot be anticipated.

In summary, the greatest improvement in the management of thyroid malignancy will follow general acceptance of the removal of discrete thyroid nodules. A papillary or an alveolar malignancy should be treated by total lobectomy and unilateral neck dissection. Postoperative roentgen therapy should be employed if nodes are involved. With an aggressive surgical approach to the management of thyroid cancer, we can anticipate an improvement in results.

# Strictures of the Common Duct

WARREN H. COLE*

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WARREN H. COLE

ABOUT two-thirds of all strictures of the common duct are traumatic in origin, i.e., due to surgical trauma. With few exceptions the histories in these cases reveal that jaundice appeared a few days after operation or a relatively complete biliary fistula developed a few days after operation. An additional 20 or 25 per cent of common duct strictures appear several months after operation and we term them inflammatory, but many of these are possibly of traumatic origin too.

It is a unique circumstance that almost all these strictures develop after cholecystectomy. Very few cases are seen following cholecystostomy, presumably because the surgeon is not working near the common duct. Likewise, few are noted following choledochostomy, presumably meaning that the common duct has been isolated so clearly that trauma is avoided.

Chronic pancreatitis accounts for 5 or 6 per cent of common duct strictures.

The most important factor in producing the injury is carelessness or haste in performing the operation (figure 1). Insufficient knowledge of anatomy, particularly of the anomalies, constitutes the second most important factor. Nowhere else in the human body are there so many anomalies as there are in the biliary tract. Third, difficulty in controlling hemorrhage develops either from failure to put a clamp on the cystic artery or from trauma to the right hepatic artery, which in itself is a very serious injury. Probably half the patients in whom the right hepatic artery is injured and ligated die because of severe hepatic damage.

It is not difficult to make the diagnosis of trauma to the common duct when the obstruction is complete. Either the patient will have jaundice and acholic stools on the second or

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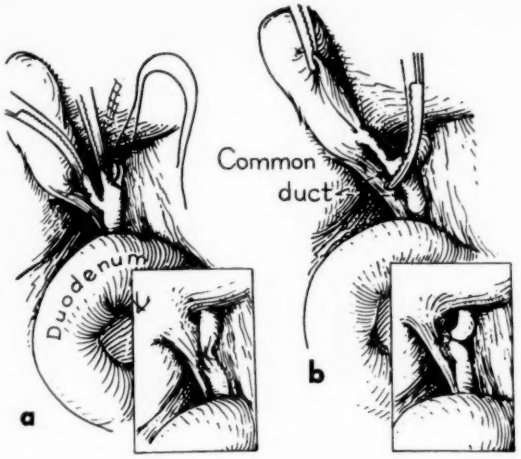
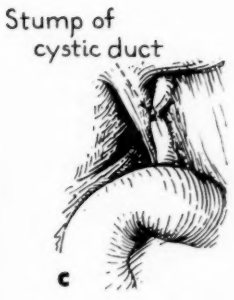
Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

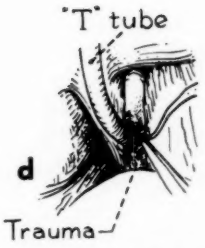



a. Transfixion with a needle.

b. Ligation with the cystic duct.



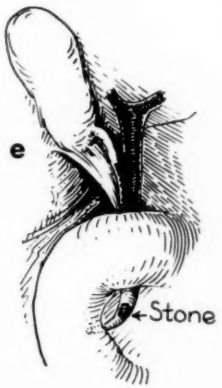

c. Ligation of the cystic duct too close to the common duct.



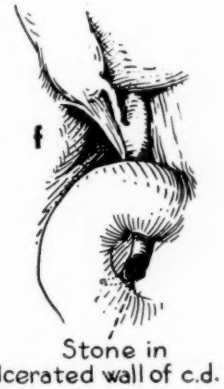

d. Chronic diffuse sclerosing pancreatitis.

FIGURE 1. Mechanisms in production of stricture of common duct.

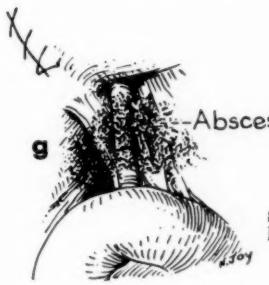
(From Cole, W. H.: Operative Technic. Reproduced courtesy Appleton-Century-Crofts.)




e. Cholangitis.




f. Ulceration of the wall by stone.




g. Abscess or local collection of bile.

third postoperative day or a biliary fistula will develop out of which most of the bile will be coming. If one is in doubt, it is very helpful to give the patient an enema and then see whether the stools are cholic or acholic. One may have to wait a day or so to get confirming evidence, because cholic stools formed before the time of the operation may be obtained with the first enema. However, these two points—namely, appearance of jaundice after the second or third day and development of a biliary fistula a day or so after operation—usually are fairly good indexes of injury to the common duct.

If seen late, the patient has a rather typical history of chills and fever with jaundice during the attacks. The pain varies greatly in severity, from intense to relatively mild. The liver is cirrhotic, and in many cases the spleen is enlarged due to portal hypertension.

Indications for operative repair of a stricture of the common duct sometimes are not clear-cut, particularly when the patient has relatively mild symptoms such as an occasional attack of pain, perhaps with chills and fever, and jaundice lasting a day or two.

I have adopted the philosophy that one

must watch the liver, that is, watch it for evidence of impaired function, to help determine when an operation is necessary for repair. Impaired liver function as indicated by elevated thymol turbidity or BROMSULPHALEIN® retention may in itself constitute an indication for surgical intervention before sufficient hepatic damage develops to reach the irreversible stage. After many years of experience with common duct strictures, I have learned that severe hepatic disease can reach an irreversible point and even proceed to a fatality even though one has corrected the stricture. The manifestations of hepatic damage may mimic those of stricture or other obstructions of the common duct.

Ordinarily, one should repair the damage as soon as the diagnosis of ligation of the duct or similar injury is made, that is, in two or three days. It is much easier to correct the damage at that time than six weeks afterward. Moreover, from the third to the sixth week following an operation the adhesions are most vascular and dense, making dissection very difficult indeed.

In doing a repair, I prefer to use the Roux Y arm of the jejunum. Before I discuss operative technic, I want to bring out a couple of points regarding diagnosis, and I can do this best by describing several cases.

A 42 year old woman underwent cholecystectomy elsewhere in February 1953. In September, pruritus, jaundice and diarrhea appeared. That is almost within the realm of the incubation time of viral hepatitis and we were not sure whether she might have this disease. The prothrombin time was 35 and went up to 86 with vitamin K. The A-G ratio was normal. The alkaline phosphatase indicated an obstructive lesion. The thymol turbidity was 6 units, and she had acholic stools. All these findings pointed toward a common duct obstruction and not liver disease. At operation a stricture was found and repaired.

A similar case concerned a 59 year old woman with a 10 year history of jaundice. Did she have cirrhosis or common duct obstruction? She had cirrhosis. Beginning in about 1943, she had dyspepsia, vomiting, intermittent acholic stools and rather constant jaundice. In 1945 an operation was performed elsewhere. At that time her liver was normal except for slight enlargement—about one fingerbreadth. The common duct was normal. The A-G ratio showed a definite trend toward reversal, and the cephalin-cholesterol flocculation was 2 plus, indicating that she had liver disease. The serum bilirubin was elevated to 7.5 mg.

She was admitted to our hospital in November 1953. Her liver was enlarged 3 to 6 cm. beyond the costal margin. Again, the A-G ratio was reversed. The prothrombin time was 46 per cent, and there was a 37 per cent retention of Bromsulphalein; the alkaline phosphatase was 10 to 14 units, the thymol turbidity was elevated 14 to 27 units, and the cephalin-cholesterol flocculation test was 3 plus. All these findings told us clearly that she had liver disease, not obstruction, as a primary diagnosis. However, in the presence of long-standing common duct obstruction, liver disease of considerable magnitude can develop. We knew she had severe liver disease but thought perhaps she might also have an obstruction. Accordingly, we operated on her; we found a nodular cirrhotic liver which explained all her trouble.

The spleen was enlarged to two or three times its normal size. The common duct was normal. The patient recovered satisfactorily from the operation, but she died a few months ago. In short, here was a patient with cirrhosis of the liver who survived 12 years after the onset of symptoms in 1943.

The case of the third patient represents probably the worst results we have ever had. She was 57 years old. Cholecystectomy and choledochostomy were done elsewhere in 1947. Six weeks afterward, intermittent jaundice developed. We operated on her in 1947 and repaired a stricture. She was well for eight months and then had attacks of pain, chills and fever, with intermittent jaundice and acholic stools. On a few occasions she had brown stools with her jaundice. She was admitted to the hospital again in June 1952. The prothrombin time was within normal limits; the cephalin-cholesterol flocculation test gave negative results; the alkaline phos-

phatase was elevated to 22 units, indicating the presence of an obstruction (yet I would warn you that the alkaline phosphatase can be unreliable). The thymol turbidity was elevated, and the A-G ratio was slightly reversed. At operation we did not find a stricture, but the liver was large and cirrhotic.

She continued to have trouble and was readmitted in March 1953. Total proteins were only 5.7 gm. per cent, the prothrombin time ranged from 30 to 95 per cent, the thymol turbidity was 11 to 23 units, and the cephalin-cholesterol flocculation was 3 plus. Shortly after this she began to bleed from numerous sources, and died a few days later. At autopsy the liver showed marked cirrhosis and considerable microscopic cellular damage.

I want to emphasize that even though we corrected the stricture satisfactorily in this case, the liver disease had reached an irreversible stage resulting in death.

What about preventing strictures during cholecystectomy? I would like to present 12 commandments for prophylaxis:

1. Obtain good exposure and do not hurry.
2. Constantly be aware of possible anomalies that may be present.
3. Isolate the junction of the cystic and common ducts.
4. Do not cut any structure until it is fully identified.
5. Do not ligate any artery in the region of the ducts until it is proved that it enters the gallbladder.
6. Ligate the cystic duct and the artery separately.
7. Control hemorrhage by compressing the right hepatic artery in the hepatoduodenal ligament.
8. Start dissection of the gallbladder at the fundus if adhesions are dense.
9. During cholecystectomy, observe the field for severed accessory ducts and ligate them.
10. Use gentle technic about the common duct to avoid trauma.
11. Maintain good asepsis to minimize abscess formation. I am sure that abscesses around the common duct occasionally result in stricture. Collections of bile will do the same; they get infected, resulting in abscess and subsequent stricture.
12. Avoid delay in surgical treatment of cholecystitis. Operate before the inflammation is so severe that surgery is dangerous.

In repairing a common duct stricture, an end-to-end anastomosis is desirable if one can find both ends, but I am learning that the sphincter of Oddi is not quite as important as we originally thought it was. Rather than risk damage sustained by splitting the pancreas to find the distal end, I use the Roux Y arm of the jejunum quite often. Dr. Richard Cattell of Boston rather strongly favors finding this distal end; I cannot do it as well as he can. I agree that one should do an end-to-end anastomosis if possible, and put in a T tube—that is, a prosthesis—but never through the suture line. In my opinion, bringing the T tube out through the suture line will almost always give rise to a recurrence. Figure 2 shows the Roux Y arm with the jejunum being anastomosed to the duct at the hilus; in this particular case we did not use a prosthesis. When the common duct is large and comparatively free from inflammation we do not use a prosthesis. We usually can get by with only one row of sutures, because this is a defunctionalized loop of bowel and two rows are not necessary as would be the case in functioning intestine. By puckering the sutures, one obtains an end-to-end anastomosis somewhat like that shown in figure 2. We have had 29 patients in whom we have done procedures of this type without a prosthesis, and results have been good in all of them up to now.

I do not mean to imply, however, that operation should always be done without a prosthesis. In certain instances a prosthesis is very definitely needed, such as when the hilar duct is small or its wall is much inflamed or when liver tissue must be penetrated (figure 3). In these cases, the prosthesis must remain in place for 9 to 12 months. A T tube stays in position readily and does not tend to become displaced as readily as a catheter does; moreover, one can split the end and turn one arm up the right duct and one arm up the left.

We have performed 187 operations on 122 patients with stricture of the common duct

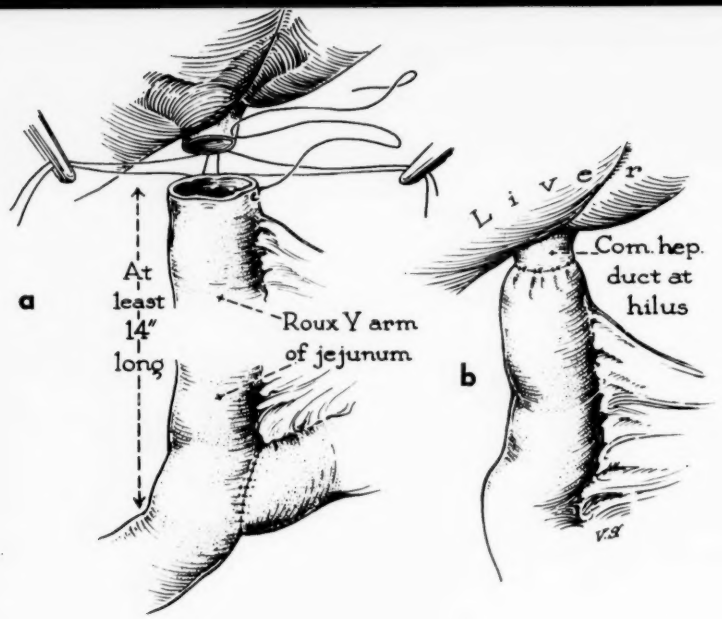



FIGURE 2. Repair of stricture by anastomosing the hilar duct to the end of a Roux Y arm of jejunum when the distal end of the duct cannot be found.

a. Interrupted mattress sutures of fine silk are taken through the common duct and jejunum as illustrated.

b. Appearance of the suture line after all sutures are tied. The hilar duct is not always as large as shown. When it is smaller, a smooth junction will not be achieved so readily. When the hilar duct is large and relatively free from inflammation we do not use a T tube or catheter for a prosthesis.

with a mortality rate of 6.9 per cent. One can get a 90 per cent good result if there is a duct extending 2 or 3 cm. outside the liver, particularly if it is widely dilated and not the seat of considerable inflammation. Contrariwise, the poor results occur in instances where there is no duct protruding outside the liver, particularly when one has to excavate into the liver to find it and when it is narrow and inflamed. The result in such cases would not be much better than 60 per cent; at least that is true in our experience.

Portal hypertension is a serious complication of stricture of the common duct. Twenty-nine patients in our series, a little more than 25 per cent, had significant portal hypertension. This complicates the surgical repair greatly because of excess bleeding, which on two or three occasions has forced us to stop the operation before the stricture was repaired. I remember in one instance 1500 cc. of blood had been transfused by the time I got through the abdominal wall. We had to stop that operation and do a splenorenal shunt first. At times I think that may be desirable.

Remember that liver disease is really the lethal factor in this condition. Whatever we do, we must try to protect the liver and repair the stricture before serious hepatic damage occurs.

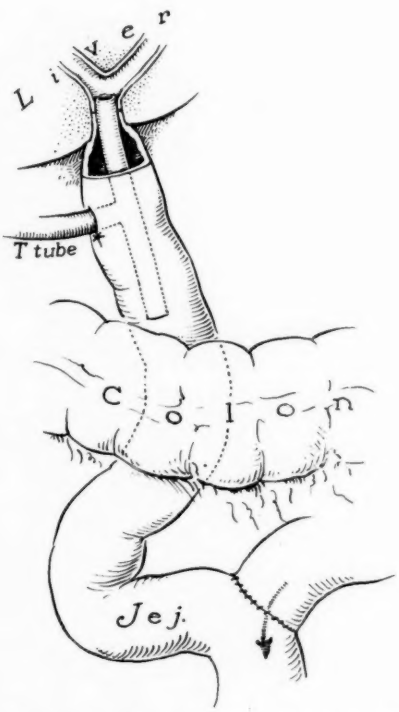



FIGURE 3. When the hilar duct is small or its wall much inflamed, or when liver tissue must be penetrated to reach the duct, we believe a prosthesis is desirable. At present we are using a T tube for this purpose particularly since the long arm through the jejunum tends to hold the tube in place. When the bifurcation of the ducts is near the suture line, the end of the tube should be split, and a half inserted into each duct.

(Figures 2 and 3 reproduced courtesy *Annals of Surgery*.)

There are a couple of patients here today, and I would like to present them now. The first one is a 39 year old man who in 1947 and 1948 had episodes of right upper quadrant pain with bloating and epigastric distress following the eating of greasy foods.

Cholecystectomy and appendectomy were done in 1948 at another hospital. Records obtained from that hospital disclose a diagnosis of chronic cholecystitis without cholelithiasis. A nonvisualized gallbladder had been reported on a gallbladder series prior to the operative procedure. Postoperatively the patient became jaundiced immediately, with dark urine and light stools, dryness of skin, and pruritus. These symptoms persisted intermittently for five years prior to admission to this hospital.

The patient's history also reveals that a son was jaundiced immediately prior to this patient's cholecystectomy and his wife became jaundiced within a few weeks afterward; the condition cleared in both cases.

When he was first admitted to this hospital in October 1953, the patient was clinically jaundiced and afebrile. His serum bilirubin was 10 to 16 mg., thymol turbidity 44.5 units and alkaline phosphatase 26.9 units, indicating obstruction (there can be high alkaline phosphatase in cases of cirrhosis, which this patient had), but the prothrombin time was 100 per cent. This illustrates that the prothrombin time is not very reliable—at least in my experience. The liver function tests I like are the thymol turbidity test, the cephalin-cholesterol flocculation, the alkaline phosphatase, the Bromsulphalein, and the A-G ratio. It seems to me we get more reliable information utilizing those tests.

An exploratory laparotomy was performed immediately because of the evidence of obstruction as well as the hepatic insufficiency which was thought to be due to extrahepatic biliary obstruction of long duration. A long cystic duct and a portion of the gallbladder were found. A T tube was inserted in the common duct. Liver biopsy was reported as compatible with cholangiolitic hepatitis.

After operation the patient continued to be jaundiced, and I would like to ask him how he is getting along now. (To the patient): How is your strength? Has it come back well?

PATIENT: No.

DR. COLE: Are you working?

PATIENT: No.

DR. COLE: Why? You don't feel up to it?

PATIENT: Well, about the time I thought I could go back to work I didn't feel like it.

DR. COLE: In other words, he was not feeling well enough to work. Have you gained much weight?

PATIENT: No, I haven't.

DR. COLE: Is your jaundice still present?

PATIENT: Yes, sir, it is.

DR. COLE: Are your stools brown or light?

PATIENT: Well, they change; sometimes they are dark and sometimes light.

DR. COLE: That is typical of cirrhosis, which is the cause of this patient's trouble; the color of the stools is very helpful diagnostically, but is variable in cirrhosis.

In retrospect, as I indicated, the principal factor here, I think, was the liver disease. The alkaline phosphatase, you will recall, was constantly elevated, indicating obstruction—true obstruction in the liver, not extrahepatic obstruction. Also the thymol turbidity was constantly elevated, pointing toward liver disease.

Dr. Doxie, do you know whether a Bromsulphalein test was done or not?

DR. DOXIE: I think his last one was about a month ago. It has remained elevated, ranging from about 10 to 20 per cent retention.

DR. COLE: That is one of the best tests for cirrhosis, whereas the thymol turbidity test is better for detecting cellular damage.

This patient had a noncalculous gallbladder removed in 1948. The absence of stones might suggest that his cirrhosis was incubating at that time and perhaps was causing his symptoms. He may have had an early cirrhosis mimicking the symptoms of gallbladder disease. He has residual jaundice and his strength is not quite back to normal, although he is eating well. How about fatty foods?

PATIENT: They bother me some, not a lot.

DR. COLE: It is sort of traditional that a patient with gallbladder disease cannot eat fatty foods, but there are a lot of other diseases which do not allow the eating of fatty foods, so do not draw the conclusion that all patients

with that symptom complex have gallbladder disease. (To the patient): Thank you.

To summarize this case, then, this patient has cirrhosis of the cholangiolitic type and a slightly enlarged liver. He is progressing fairly satisfactorily at present; you are familiar with the prognosis.

The next patient was 24 years old when she came to the hospital complaining of pain in the right upper quadrant radiating to the back, between the scapulae, of two days' duration. She had her first attack during pregnancy.

Your doctor said that you had gallbladder disease?

PATIENT: That is right.

DR. COLE: She had several such attacks. On two or three occasions she had chills and fever. She did not have jaundice and had not noted any scleral discoloration.

Physical examination at that time disclosed tenderness in the right upper quadrant but otherwise was noncontributory.

In 1949 cholecystectomy was done, and by the third postoperative day the urine was dark in color and the sclerae were icteric, indicating an obstructive mechanism in the common duct. About 20 days later an end-to-end anastomosis was done, is that right, Dr. Gallagher?

DR. GALLAGHER: Yes. The common duct could not be identified distally. The hepatic duct was found. The duodenum was opened, a probe was passed up from the ampullar side, and the distal common duct was found markedly strictured. A T tube was introduced into it and pulled down through.

DR. COLE: The patient had trouble after that—intermittent attacks of pain. (To the patient): This pain was severe?

PATIENT: That is right.

DR. COLE: And you had chills and fever, and acholic stools, that is, they were light?

PATIENT: Yes.

DR. COLE: How long did each attack last? Twenty-four hours?

PATIENT: Oh, no, they usually gave me something for the pain, but the attacks disappeared rather quickly sometimes.

DR. COLE: She had numerous attacks in that interval of about a year while she was under observation, and then she had a second operation and another end-to-end anastomosis.

DR. GALLAGHER: At the second procedure, again the stricture was found in the common duct at the site of the first-placed T tube which had been removed six months postoperatively. Nine months after the first exploration the second procedure was done and the duodenum was freed up immediately, the pancreas was split, the distal common duct was found, and a new T tube introduced and a new end-to-end anastomosis made.

DR. COLE: If one finds the two ends readily, I think it is desirable to do an end-to-end anastomosis. Since the operation she has had no symptoms.

DR. GALLAGHER: A little pain now and then, but no jaundice.

DR. COLE (to the patient): Your stools are brown?

PATIENT: Yes.

DR. COLE: We know these patients do have an occasional attack after operation, but with progress like this we feel sure she is going to have a fine result.

# Current Practices in the Diagnosis of Tuberculosis

*A Symposium From the Mayo Clinic and Mayo Foundation,* Rochester, Minnesota*


- Introduction
  DAVID T. CARR, *Section of Medicine*
- Diagnostic Value of Tuberculin Tests and Certain Blood Tests in Tuberculosis
  FRANK D. MANN, *Section of Clinical Pathology*
- Problems in the Histologic Diagnosis of Tuberculosis
  JOHN R. McDONALD, *Section of Surgical Pathology*
- The Bacteriologic Diagnosis of Tuberculosis
  LYLE A. WEED, *Section of Bacteriology*
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# Introduction

DAVID T. CARR

During the last 10 years there have been remarkable advances in the treatment of tuberculosis. With the discovery of streptomycin began an era of antituberculosis therapy characterized by the development of new drugs faster than physicians could learn to use the old ones properly. As a result, the phthisiologist has available today half a dozen antimicrobic agents from which to choose the combination most efficacious for each patient.

To this have been added refinements in surgery, particularly thoracic surgery, making it frequently possible to remove surgically that disease which cannot be cured medically.

As a result the death rate from tuberculosis has declined sharply in Minnesota and throughout the United States to the lowest figures ever recorded.

This gratifying accomplishment has given rise to an unwarranted optimism that at long last tuberculosis has been controlled and is no longer a serious problem. Further consideration of the problem indicates that this is not true and suggests that the death rate is no longer an adequate yardstick for the problem of tuberculosis, just as the death rate would be a poor index by which to measure the problem of the common cold or hay fever, to mention only a couple of common diseases.

The new case rate is a much more valid measurement of the tuberculosis problem, in spite of gross inaccuracies in the data available due to variations in habits of reporting cases of tuberculosis from state to state and from year to year in the same state. The reports available from official agencies indicate that the diagnosis was made in about 2000 new cases in Minnesota in 1953 and the figure for the entire United States was more than 100,000. It is obvious, therefore, that tuberculosis is not yet controlled and will be a significant medical problem for years to come.

Each newly discovered patient with tuberculosis is entitled to specific antituberculosis treatment without delay. This is possible only when a specific diagnosis is made without delay. The technics discussed in this symposium should be applied vigorously whenever tuberculosis is suspected. Only when this is done will the diagnosis of tuberculosis be established promptly and a proper regimen of treatment initiated.

# Diagnostic Value of Tuberculin Tests and Certain Blood Tests in Tuberculosis

FRANK D. MANN

THE incidence of both clinical and subclinical tuberculosis has decreased in recent years, so that at present the majority of young adults have not acquired cutaneous sensitivity to tuberculin. Hence, the tuberculin skin test has become of far greater diagnostic value than it was when a majority of the population demonstrated positive cutaneous reactions to tuberculin early in life. Furthermore, it is now recognized that many lesions resembling tuberculosis clinically, roentgenologically and even histologically are actually due to other organisms.

### *The Tuberculin Test*

Because of the change in status of the tuberculin test, it has been worthwhile to give attention as to how its greatest precision can be obtained. The patch and the scratch (von Pirquet) methods of performing the tuberculin test, although valuable in mass surveys, generally are considered to be less accurate than is the intradermal (Mantoux) test, which permits administration of an exact dose of tuberculin. The significance of an exact dose obviously depends on the reproducibility of the preparation of tuberculin used. Because of the evidence originally presented by Seibert and co-workers[1] that the purified protein derivative (PPD) of tuberculin is more reproducible than is old tuberculin (OT), PPD has been used routinely at the Mayo Clinic for more than 15 years. The original first-strength dose of PPD recommended by the National Tuberculosis Association was 0.00002 mg., whereas the second-strength dose was 0.005 mg. Subsequent experience has shown that the initial dose may be somewhat larger, usually 0.0001 mg., except when there is reason to suspect unusual sensitivity on the part of the person being tested. Experience at a number of institutions is in good agreement that 90 to 95 per cent of persons who have proved tuberculosis show positive reactions to the injection of 0.0001 mg. of PPD; more than 99 per cent of such persons react positively to the second-strength dose of 0.005 mg.

Evidence exists that the increased incidence of positiveness to the second-strength dose is obtained at the expense of a certain number of false positive reactions. Palmer,[2] in a study of 22,000 student nurses throughout the United States, noted that positiveness to a dose of 0.0001 mg. of PPD was strongly correlated with a history of contact with tuberculous persons. However, positiveness to a dose of 0.005 mg. of PPD was not correlated with a history of contact but was strongly correlated with the place of residence. The results of this and other similar studies are believed due to sensitization of persons in certain localities to organisms antigenically related to the tubercle bacillus. This possibility must be taken into account in interpreting positive results of second-strength tuberculin tests.

It remains highly controversial whether PPD or OT is to be preferred; the foregoing discussion represents the personal preference of my associates and me. The United States Public Health Service has used PPD in extensive surveys. OT often has been preferred for tests after vaccination with the bacille Calmette Guérin (BCG), since this type of tuberculin allegedly gives stronger reactions after such vaccination, which usually induces a far less degree of cutaneous sensitivity than does naturally acquired tuberculous infection.

This consideration of increased sensitivity obviously must be balanced against the evidence that the tuberculin test can be nonspecific.

The foregoing encouraging statements as to the value of the tuberculin test must be tempered by recognition of some possible sources of error and risk. Even PPD probably is not absolutely reproducible; it has been reported that some batches of this material detect less than 50 per cent of reactors.[3] The technical error of injecting part of the dose subcutaneously can diminish the sensitivity of the test; considerable care is required to be sure that the dose of tuberculin is introduced quantitatively in certain persons who have unusually thin and delicate skin. The recent study of Guld[4] dealt with this and other sources of error. An occasional person may show an excessive reaction to 0.0001 mg. of PPD; preliminary clinical inquiry should be made to uncover the potentiality of unusual sensitivity, and a smaller initial dose should be chosen if such a possibility appears likely. Despite these difficulties, an excellent case can be made out for careful performance of the Mantoux test with every routine physical examination to supplement, although obviously not to supplant, the roentgenologic examination of the thorax.

### *Blood Tests*

In the past, numerous attempts to develop complement fixation tests for tuberculosis have failed due to the high incidence of false positive reactions. A more recently introduced immunologic procedure, namely, the tuberculin hemagglutination and hemolysis test, has given similar false positive reactions in the hands of several investigators but it remains under consideration. Middlebrook and associates[5] recently have reported modifications in the technic of this procedure; their changes involve purification of the tuberculin and adsorption of the serum with *Histoplasma* organisms. While it would appear conceivable that this test yet may be developed to give high specificity, it also may be considered too complicated for use in most routine laboratories. The use of the erythrocytic sedimentation rate to follow the course of tuberculosis is too well known to require comment except to note that the incidence of normal sedimentation rates in active tuberculosis is appreciable, being 15 per cent according to a recent report.[6]

Various other procedures for detecting alterations in plasma proteins produced by tuberculosis have been tried in order to follow the activity of the disease. Parenthetically, it may be noted that many of the so-called tests for cancer, such as the Huggins test, are fully as "good" for tuberculosis as they are for cancer, although their use in detecting tuberculosis has not been advocated.

Extensive and encouraging observations on the measurement of the viscosity of plasma as a test for the activity of tuberculosis have been reported by Houston and co-workers.[7] These authors used a method that has considerable accuracy but it is rather laborious for the average clinical laboratory. The more commonly used Hess method has proved highly inaccurate in the hands of most workers. I[8] have developed an accurate method for determining viscosity of plasma that is three or four times as laborious as is the sedimentation rate; evidence is not available thus far that it is any better than the sedimentation rate in measuring tuberculosis activity. However, it should be kept in mind that the determination of viscosity and other precise physicochemical measurements on plasma, possibly even electrophoresis, some day may be applied practically to supplement the sedimentation rate.

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# Problems in the Histologic Diagnosis of Tuberculosis

JOHN R. MCDONALD

MYCOBACTERIUM TUBERCULOSIS in the tissue incites tubercle formation. This reaction is referred to as a granulomatous reaction and the result as a granuloma. A tubercle formation consists of an oval or roundish collection of histiocytes in which the cells are arranged like the spokes in a wheel. At other times the histiocytes do not have any organization. Frequently aggregations of histiocytes occur; these are then called "foreign-body giant cells." The histiocytes in a tubercle are sometimes referred to as "epitheloid cells" because of their superficial resemblance to epithelium. Lymphocytes usually surround such a tubercle and may be admixed with it. Necrosis may or may not be found in the tubercle. As the granulomatous process progresses, several tubercles may coalesce to form a caseous mass. When this occurs, the tubercles are no longer discrete tubercles. A histologic tubercle or granuloma suggests the diagnosis of tuberculosis but, of course, agents other than *Myco. tuberculosis* can produce a granuloma. If this is borne in mind, it will become evident that the diagnosis of tuberculosis cannot be made histologically without finding the acid-fast bacilli, in either the sections or smears, or preferably on culture of the organisms and test of their virulence in guinea pigs.

A granuloma is caused by a great many agents. There are also some granulomas, such as Boeck's sarcoid, for which no etiologic agent has been determined. Although many of the agents which produce granulomas are bacteriologic, not a few of these agents are chemical.

### *Nonbacterial Agents and Lesions*

A fairly wide variety of nonbacterial agents can produce granulomas. Some of these agents are silicon, silicates, beryllium and various types of lipids.

*Silicon*—Owing to the fact that silicon dioxide is inhaled, the lesions of silicosis are seen almost exclusively in the lungs. The individual lesion is a noncaseating tubercle which tends to undergo extensive fibrotic change. The best way to demonstrate silicon is by micro-incineration and subsequent examination of the incinerated material with polarizing plates.

*Silicates*—Among the diseases due to the silicates are pulmonary asbestosis and talc granuloma. Talc, as used in dusting powder in the operating room, contains, among other things, silicates. These will lead, in wounds or in the peritoneal or pleural cavity, to the development of noncaseating tubercles which, in turn, will lead to the development of adhesions near the center of which doubly refractile elements can be demonstrated.

*Beryllium*—Berylliosis is a rare disease which has been seen because beryllium is used in fluorescent light bulbs. The disease, which is characterized by granuloma formation, is most commonly seen in the lungs because of the inhalation of material. Although there are certain histologic details which, with the history, would suggest the diagnosis of beryllium granuloma, the definitive diagnosis can be arrived at only by highly technical methods.

*Lipoid granuloma*—The various lipids which produce granulomas can be divided into those of animal, vegetable and mineral origin. The lipids of hydrocarbon nature produce a more intense reaction than do the others. Most noteworthy in respect to the granulomas produced by the petroleum products is the fact that a latent period may be present between the introduction of the par-

affinlike material into the body and the production of a granuloma.

### *Bacterial Granulomas*

It is impossible to make a histologic diagnosis of the specific bacterium causing a granuloma unless the organism can be demonstrated and classified. Even when the organisms can be demonstrated in ordinary histologic sections, it may be impossible to classify them properly because of the similarity of one type of organism to the other. For instance, *Histoplasma capsulatum* may simulate *Leishmania*. *Blastomyces* has been mistaken for *Coccidioides* or *Cryptococcus*. Such mistakes will be less common if bacteriologic methods of identification are used.

Too frequently organisms are not found in the histopathologic sections of the granuloma when ordinary histologic stains are utilized. Several factors are responsible for this:

1. The organisms may be dead. In such cases there is frequently little evidence of histiocytic response around the necrotic or fibrotic site. An example of this is the lesion which is frequently referred to as the Ghon tubercle or Ghon complex. Although this lesion was originally described by Ghon as being the end stage of primary tuberculosis, no bacteria can be demonstrated in the end state, which represents a healed condition. My colleagues and I have seen a few examples of lesions which resemble Ghon tubercles and in which a few viable organisms of *C. immitis* were demonstrable culturally; thus it seems reasonable to suppose that some lesions which are called "Ghon complex" are due to organisms other than the tubercle bacillus. It seems better to think of the Ghon complex as being the result of a healed or healing granuloma of indeterminate etiologic nature unless organisms can be demonstrated in the lesion.

2. The organisms may be too few to be seen in histologic sections. In the portion of the various bacterial granulomas that can, as a rule, be demonstrated histologically, such as those in histoplasmosis, coccidioidomycosis and blastomycosis, organisms may not be found in sections stained by the routine methods employed in a laboratory for pathologic diagnosis. Bacteriologic examination of such granulomas offers the only way in which the organisms can be demonstrated. It is impossible to state the exact percentage of the various diseases in which organisms are not found by the ordinary careful search, but, in our experience, it is sizable.

3. Organisms may not be visible with the ordinary stains. Examples of diseases in which this occurs are sporotrichosis and tuberculosis.

### *Comment*

The histologic diagnosis of tuberculosis then should not be made without supporting bacteriologic evidence. If bacteriologic studies cannot be made, the demonstration of acid-fast bacilli in stained sections within the tubercles, although not absolute proof, will provide strong evidence in favor of a tuberculous etiology.

## The Bacteriologic Diagnosis of Tuberculosis

THREE procedures are commonly employed in the bacteriologic laboratory to obtain information important in the diagnosis of tuberculosis: (1) use of an acid-fast or auramine stain, (2) cultures to isolate the organism, and (3) the inoculation of guinea pigs to produce lesions of tuberculosis.

### *Acid-fast Stain*

Staining material from a patient suspected

of having tuberculosis is advantageous because information may be obtained quickly when this procedure is used. Only a few minutes are required and if typical organisms are found, the information when considered in conjunction with clinical information at times may be sufficient to warrant isolating the patient to prevent dissemination of the disease to other people and instituting chemotherapy. It is important to recognize two limitations to this technic, however: (1) Avirulent or saprophytic acid-fast bacilli are fairly common in certain materials, such as gastric washings and scrapings from cutaneous sinuses around the neck, axilla, groin and perineum. Occasionally, but much less frequently, such organisms are also found in sputum or emulsions of tissue. The finding of acid-fast bacilli of the size and shape of the tubercle bacillus does not establish the diagnosis of tuberculosis. (2) In experience at the Mayo Clinic acid-fast bacilli are found in smears from only about 55 per cent of the specimens proved by culture or guinea pig inoculation to contain them. Therefore, a smear negative for acid-fast bacilli is not sufficient basis to permit the diagnosis of tuberculosis to be ruled out completely.

LYLE A. WEED

### *Cultures*

Cultures for tubercle bacilli are satisfactory when properly performed. This means that better results will be obtained if two or more media and at least four tubes are used; the media should be fresh (that is, not stored for several weeks or months prior to use), and the examiner must exercise considerable skill in interpreting the results. Since cultures deal with living organisms which have adapted themselves to various conditions in the patients, it is not surprising that the cultural features are variable. Many of the colonies begin to appear after incubation for about two to three weeks; others appear only after four to six weeks. Saprophytes are likely to appear in a few days but may require two, three or four weeks before appearing and at first may closely resemble the cultures of tubercle bacillus.

Because of the variability of the cultural features, a virulence test is done routinely at the Mayo Clinic on each strain isolated and suspected of being virulent. Many cultures are so obviously cultures of saprophytes, as judged by many studies in the past, that virulence tests are not performed on them and the organisms are reported merely as saprophytes unless they are isolated from closed lesions, such as those in bone, bursa, lymph node, kidney, spleen, liver or lung. However, because of the psychologic, sociologic and economic importance to the patient when a diagnosis of tuberculosis is made, it is important to be as certain as specific information will allow before such an interpretation is made. Occasionally a culture appears entirely characteristic of virulent *Mycobacterium tuberculosis*, but repeated tests in animals give negative results. For this reason cultures thought likely to be virulent are reported "positive for acid-fast bacilli" and not as "positive for *Myco. tuberculosis*," the latter being stated only after completion of the virulence test. This alerts the physician but still does not make a final commitment which is possible only after the test for virulence is completed.

Rapid methods of growing tubercle bacilli have been devised and widely favored at various times, but careful scrutiny of the results indicates that they are hazardous, very technical or time-consuming and therefore impractical for routine work. They provide only preliminary information at an early date and the final reporting requires time comparable with that required in this clinic when the Petragnani and Loewenstein-Jensen media are used. The so-called rapid technics for culture, therefore, cannot at present be considered a real improvement for routine diagnostic work.

### *Guinea Pig Inoculation*

Guinea pigs used for the diagnosis of tuberculosis at the Mayo Clinic are raised at the Institute for Experimental Medicine in a sepa-

rate building and with strict regulations that no one is allowed in the quarters except the caretakers. The food and general housing facilities of the animals are carefully guarded to prevent various infections, including, of course, tuberculosis. This eliminates work and time in quarantining and in testing each animal with tuberculin prior to use. During the past seven years, with approximately 38,000 specimens, the correlation between the results of animal inoculation and cultures has been close. This indicates that so far tuberculosis has not been introduced into the herd. Also there has been no evidence of tuberculosis in those animals from the herd used for experiments which have not dealt with tuberculosis.

Two guinea pigs are inoculated with the material from a patient; one is inoculated subcutaneously with one-half of the inoculum, the other intraperitoneally with the remaining portion. After four weeks, the animal inoculated intraperitoneally receives 0.5 cc. of undiluted OT subcutaneously. About 75 to 80 per cent of animals later proved to have tuberculosis will die within 24 hours. The animals which die after receiving OT are examined and a record of the extent and kind of lesions made. If they are grossly characteristic of tuberculosis and stains of material from the lesions show acid-fast bacilli, a diagnosis of tuberculosis is made. If the smears are negative for acid-fast bacilli, aliquot portions of the lesions are cultured for acid-fast bacilli, fungi, *Brucella* and other common bacterial organisms to determine the cause of the lesions. If the animal does not react to tuberculin, both that one and the one inoculated subcutaneously are allowed to go eight weeks from the time of inoculation. They are then killed and examined.

All animals dying during the eight week interval are examined to determine whether death may be the result of an infection (tuberculous or nontuberculous) originating from the clinical material, and the procedure therefore may be as important in establishing some other diagnosis as it is in ruling out cases of tuberculosis.

Sometimes the lesions observed at eight weeks are equivocal and it becomes necessary to isolate (or reisolate) the organism from the animal lesions and attempt to produce lesions in a second set of animals. This is time-consuming but important for the benefit of accurate diagnosis.

Virulence tests on cultures are made by inoculating both animals intraperitoneally. Subcutaneous inoculation of virulent tubercle bacilli leads to the formation of large ulcers which are a great hazard to the caretakers and may result in undesirable infection of other animals. This rarely happens with clinical material used as the inoculum.


***Summary***

Three procedures used in the bacteriologic laboratory may give important information regarding the diagnosis of tuberculosis.

The positive auramine stain for acid-fast bacilli gives suggestive information but does not establish an unequivocal diagnosis nor does a negative stain rule out the possibility of tuberculosis.

The culture technic is satisfactory for isolating acid-fast bacilli, but an occasional strain is encountered which grows like tubercle bacilli although it is avirulent. The reliability of this procedure depends on the scientific integrity and skill of the person examining the cultures.

The most reliable bacteriologic criterion of tuberculosis is the demonstration that the clinical material, or the culture from it, can produce tuberculosis in guinea pigs. While the interpretation of cultures and the result of the virulence test on the organism agree fairly closely, there is still enough disparity between them so that it is important for the patient's benefit to use every facility known to assist in making as accurate a diagnosis as possible and a virulence test on cultures is done with this in mind.

No valid evidence is at hand to indicate that a person may be a normal healthy carrier of the tubercle bacillus similar to the carrier state in diphtheria or typhoid fever. Hence, isolation of virulent acid-fast bacilli is prima-facie evidence of active tuberculosis.

# Roentgenologic Aspects in the Diagnosis of Pulmonary Tuberculosis

COLIN B. HOLMAN

DIAGNOSTIC roentgenologic methods have probably been used more extensively in the study of pulmonary tuberculosis than in the evaluation of any other single disease process. The literature on this subject is likewise probably as voluminous as on any other single medical subject. This continues to be true in spite of the fact that the death rate from pulmonary tuberculosis has reached a low figure. It is interesting, therefore, to consider the role of roentgenology in solving the problems of tuberculosis as they exist today.

This tool is applied in two related fields: the mass survey method of case finding and the use of particular technics as aids in the proper understanding of specific cases.

### *The Mass Survey*

The magnitude of survey work is indicated by the fact that in 1946 more than 6 million of these examinations were undertaken and in 1950, 15 million were performed. In all, about 50 million studies have been made during the five years from 1946 through 1950.[1] About 8.5 per cent of the entire population of the United States has been examined annually during these years.[2] About 1 per cent of those examined had roentgenograms which indicated the presence of active pulmonary tuberculosis.[3,4]

Although the efficacy of an initial mass survey is established, its limitations should be appreciated, in order that it may be as effective as possible. First it should be understood that for economic considerations photofluorograms have to be used; these films are small, usually 35 or 70 mm. in size. It is easy to understand that minimal lesions may be overlooked in these small roentgenograms, as the discrepancies in evaluating minimal lesions are rather large among trained interpreters even when the large roentgenograms of the chest, measuring 14 by 17 in., are employed. Therefore, it is necessary that the evaluation of these miniature roentgenograms be entrusted to trained observers and that, if possible, all roentgenograms should be inspected by two or more specialists in this field.

Among the factors which limit the value of this method there is the variability in interpretation among observers together with the variability in disease pattern and a lack of definite knowledge of the disease process.[5]

If a lesion is suspected, the diagnosis is not made on the basis of the miniature film. About 2 to 7 per cent of those examined in a mass survey are requested to obtain regular roentgenograms of the chest, and of those so urged, about 80 to 90 per cent respond. The large roentgenograms show a suspicious-appearing lesion in about 0.6 to 2.0 per cent of the entire group. Thus in most surveys active tuberculosis is found to exist in about 1 in 1000 people so examined, and of these, 85 to 90 per cent are unknown to the local health authorities.[5]

The economic value of such surveys is indicated by the experience at the Harvard Public Health Chest Clinic.[6] In a survey of more than 30,000 apparently normal individuals, 1.5 per cent of the 70 mm. photofluorograms suggested the possibility of active pulmonary tuberculosis. Seventy-two persons were proved to have active lesions. The cost of diagnosis per case of active tuberculosis was calculated to be $300. This should be compared with the $3700 it would cost for 330 days of hospitalization for any one person with tuberculosis infected by an unrecognized source.

### *Other Diagnostic Uses*

Many hospitals are now making routine

chest roentgenograms on all patients admitted. In one general hospital averaging 10,000 annual admissions, during one year 10 unrecognized cases of active tuberculosis, 200 cases of reinfection type of tuberculosis of undetermined significance, 17 thoracic tumors and 212 cardiovascular abnormalities were discovered by this procedure.[7]

### *Special Information*

Once a lesion is discovered, diagnostic roentgenologic procedures guide the clinical evaluation and treatment of the individual. It is not always possible to judge the activity of a lesion from roentgenologic examination alone, but it is the best single method of determining the presence of a lesion and demonstrating its location. It is also of considerable help in following the progress of the lesion.

The roentgenologist is concerned with evaluating the type of tuberculous lesion present, judging any complicating features and recognizing any coexisting lesions. Thus he must be acquainted with the pathologic features of tuberculosis and also must have wide experience in recognizing other diseases which alter the thoracic roentgenogram; in addition, he must be familiar with all the technical factors which alter the shadow representation produced on the film.

Complicating features include such processes as bronchial occlusion by either intrabronchial or extrabronchial disease, bronchiectasis, and the changes produced by various forms of therapy. Use of antimicrobial therapy in the treatment of the disease complicates the interpretation of the roentgenograms. In a series of 187 patients treated with streptomycin, it was found that exudative noncaseous and caseating lesions could not be distinguished unless the appearance of cavitation could be detected within the exudative lesion. Also progression of a productive phase was found to be indistinguishable from the initial exudative phase. In the course of therapy with streptomycin, cavities were seen to disappear with alleviation of bronchostenosis.[8] Coexisting disease processes, such as bronchogenic carcinoma and active pulmonary tuberculosis, result in atypical changes in a roentgenogram which may not suggest progressive tuberculosis.[9] It has even been surmised that in some cases carcinoma may be related to, and be preceded by, the epithelial changes associated with tuberculous bronchiectasis.[10]

*Special methods*—In order to evaluate these and other problems, special roentgenographic methods of investigation are being applied. Of these, the most common is the use of stereoscopic roentgenograms. In some institutions the use of this method is a routine procedure in nearly all roentgenologic examinations of the thorax. Its value is well known.

Many lesions, especially those occurring in the upper lobes, can be better evaluated when the lordotic technic is employed. Stereoscopic views are made with the patient leaning far backward, with the shoulders touching the cassette. This results in the projection of the apexes of the lungs below the obscuring shadows of the clavicles and first ribs (figure 1a and b).

One of the most valuable procedures is the body-section technic. Here the x-ray tube and cassette are moved synchronously in opposite directions in parallel planes, so that only one plane of the interposed body remains in focus. By this method one may in effect "cut through the lesion" and produce serial roentgenographic sections. This technic is of great value in demonstrating the walls of cavities, calcific deposits, the outline of the tracheobronchial tree, and the depth and direction of certain structures. It is especially valuable in the localization of disease before surgical resection and in such cases is preferred to the technic of oil bronchography.

The advisability of instilling iodized oil in the tracheobronchial tree of patients who have tuberculosis is open to question. The advocates of this procedure suggest that it may be of value in demonstrating the extent and type of the lesion in those patients in whom operation is contemplated. It may demonstrate the course, contour, caliber, mucosal relief pattern and the character of the bronchi, and in some cases may demonstrate cavitation. There can be no doubt that as far as roentgenologic diagnosis is concerned it is the best technic available to show the presence of bronchial in-

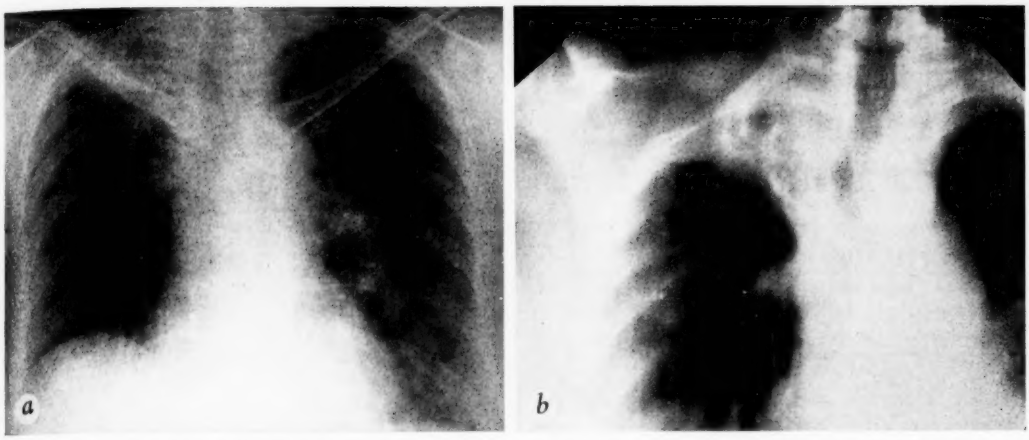

FIGURE 1a. Standard postero-anterior roentgenogram of the thorax. There is a poorly defined pathologic process in the upper medial portion of the right lung field. b. Anteroposterior view made with patient in the lordotic position. The pathologic process in the right upper lobe is more easily identified.

volvement. It may indicate bronchial obstruction, as well as bronchiectasis. However, there is danger of bronchogenic spread and dissemination of the infection, as a result of the introduction of the medium, especially in patients who have roentgenographically unstable lesions or in whom sputum examinations show the presence of tubercle bacilli.[11]

In recent years some effort has been made to apply pulmonary angiography to the diagnosis of intrapulmonary disease processes. However, from a recent study of postmortem material, it was concluded that it is impossible on this basis to distinguish tuberculosis, silicosis, bronchial carcinoma, pulmonary emboli, lung abscess, bronchiectasis and pneumonia.[12]

### *Guide to the Course in Tuberculosis*

Roentgenography of the thorax often provides an important guide in the prognosis of pulmonary tuberculosis. Studies have indicated, as one would expect, that progression rates are higher in those patients whose roentgenograms show a lesion in the so-called exudative or productive phases than in those whose examinations demonstrate fibrotic and calcified lesions.[13] In addition, the prognosis of the disease after certain therapeutic procedures, such as pneumothorax, has been extensively studied, especially with reference to complications which are recognized by means of these roentgenograms. These include, for example, the development of empyema and the unexpandable lung.[14] Thus roentgenography gives quite as important aid in managing and treating this disease as it does in recognizing its presence in the first instance.

In a previous symposium[15] the function of roentgenography in diagnosing pulmonary tuberculosis was summarized. The present discussion serves to indicate that following the discovery of a pulmonary lesion by roentgenography of the thorax, and after it has been identified as tuberculosis by proper laboratory procedures, the various usual and unusual applications of the roentgenologic method serve to indicate the location, extent and probable pathologic type of the lesion. It provides a safe and reliable method for following the progress of the disease under medical management and contributes important information for the successful preoperative and postoperative care of the patient.

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# The Clinician's Responsibilities in the Diagnosis of Tuberculosis

BRUCE E. DOUGLASS

To the clinician falls the final responsibility for the diagnosis of tuberculosis. The diagnosis cannot be established solely on the roentgenologist's report of a pulmonary cavity, the bacteriologist's finding of acid-fast rods in sputum, or the pathologist's report of a caseous granuloma or a strongly positive tuberculin reaction. All these findings, and others, must be examined carefully in the light of the total clinical picture. A patient sick with fever, cough and expectoration who has a thick-walled pulmonary cavity and reacts positively to the tuberculin test probably will be found to have tuberculosis, although the possibility of fungous infection, pulmonary abscess, infected cyst or necrotic neoplasm also must be considered. The differential diagnosis of noncavitary lesions is an even more complex problem.

As in many other diseases, one single feature of the case may provide the key to diagnosis when all other evidence is equivocal. In no other area is this more true than in the medical history. A history of idiopathic pleural effusion, recent conversion of the tuberculin reaction from negative to positive, or contact with a tuberculous patient may be of the greatest value in diagnosis.

A diagnosis of tuberculosis must be considered only presumptive until the bacteriologist not only isolates tubercle bacilli but also demonstrates their pathogenicity. Unfortunately, these tests are slow to be completed, and the clinician often must establish and act on a working diagnosis while awaiting this all-important information. The management of patients suspected but not yet proved to have tuberculosis is difficult, and many factors must be taken into consideration. The tuberculin skin test may be helpful in deciding on the course of action. If the tuberculin reaction is negative, and there is no obvious explanation for its being negative, such as critical illness or senility, the clinician probably is not justified in advising intensive tuberculosis therapy until bacteriologic proof is available. The younger the patient, the more helpful the tuberculin test. A positive tuberculin test in a 15 year old boy weighs more heavily in diagnosis than does such a reaction in a man of

50 years. Given such patients having similar pulmonary lesions, one might justifiably begin treatment in the youngster but defer it in the adult, pending the results of bacteriologic tests.

Generally speaking, one prefers to err in prescribing antimicrobial therapy for too many patients rather than for too few. While bacteriologic confirmation of diagnosis is awaited, it seems better to treat several patients needlessly than to delay treatment in any patient whose bacteriologic tests are likely to afford a proved diagnosis after five or six weeks. Modern regimens of chemotherapy are relatively free of serious side effects, particularly during the first weeks of treatment.

The indications for advising transfer to a sanatorium are not always clear-cut. Equal suspicion of active disease in a schoolteacher, a retired bachelor and a waitress might require differing courses of action. Immediate isolation of the teacher and waitress would be of greater importance to the public health than isolation of the elderly man. The presence of children in the patient's home demands more careful consideration of sanatorium care than if the patient has no intimate contact with others. Nor are all persons who harbor tubercle bacilli of equal danger to others. The patient having minimal disease who neither coughs nor expectorates certainly constitutes a minimal public health hazard. The same is true of patients with most types of extrapulmonary tuberculosis.

Many of the problems relating to the disposition of patients suspected of having, but not yet proved to have, active tuberculosis will be solved when our colleagues in bacteriology develop a practical and reliable method of demonstrating tubercle bacilli by culture in a matter of days rather than weeks.

One of the clinician's responsibilities is to be mindful of the possibility of tuberculosis in his handling of apparently healthy persons as well as patients who present diagnostic problems. The disease may be entirely asymptomatic and its manifestations variable; it may occur in any organ or system. Pulmonary tuberculosis may coexist with other lesions, such as carcinoma, cyst and silicosis. Tracheal or bronchial tuberculosis may be far advanced without altering the appearance of the chest roentgenogram. Ocular tuberculosis is difficult to prove but may show good response to specific therapy. Tuberculous peritonitis, enteritis and endometritis have probably been overlooked more often than detected. It has been shown amply that "idiopathic" pleural effusions in young individuals having positive tuberculin reactions are usually a result of pleural tuberculosis and should be treated intensively even though bacteriologic proof of infection often is not possible. Although we are accustomed to regarding tuberculosis as a chronic infection, it may cause acute illness also; tuberculous pneumonia, tuberculous laryngitis and miliary tuberculosis are acute manifestations often diagnosed too late for optimal therapeutic results and protection of intimate associates.

Early diagnosis of tuberculosis could be improved by including the tuberculin test as a feature of annual general examinations. Persons known to have become positive to tuberculin since the last test could then be studied especially carefully for evidences of clinical tuberculosis.

Another of the clinician's responsibilities is to perform or arrange for suitable tests when tuberculosis is suspected. The tuberculin test is highly accurate in excluding tuberculosis, but it is surprising to note how frequently it is not employed in instances in which it could provide invaluable information. No controversy as to whether a patient might have tuberculosis is worth pursuing unless the result of a complete tuberculin test is known.

The decision as to whether a patient has active pulmonary tuberculosis sometimes is based on a single sputum test. More often than not, this examination involves only microscopic inspection of a smear. This kind of test is by no means adequate. For microscopic tests to be meaningful, the sputum should be copious and thick and a series of specimens should be examined. It is equally unmeaningful to order or perform cultures of sputum specimens of poor quality. The physician should not rely on negative sputum smears or cultures unless he knows that the material was adequate for these types of examination. Cul-

tures of gastric content should be undertaken when the quality of the sputum specimens is questionable. The practice of assessing the results of treatment and carrying out the rehabilitation of a patient on the basis of an occasional incomplete examination of an inadequate sputum specimen is not in the patient's best interest.

Although through the ages the pathologist has had prior claim to all specimens removed at operation, we now recognize the extreme importance of providing the bacteriologist with a fair share of untreated tissue in cases of inflammatory processes. By direct microscopic study of a granulomatous lesion the bacteriologist often can confirm the pathologist's diagnosis by identifying acid-fast bacilli, thus providing a reliable diagnosis in a few hours. Although in the laboratories of the Mayo Clinic further studies are routine, it is the clinician's responsibility to be sure that suitable culture or inoculation studies are carried out.

The problem of diagnosis begins again in patients whose tuberculosis apparently has been arrested. Unfortunately, there is always the danger of reactivation of disease. Since prolonged treatment with antimicrobial agents often results in the development of drug resistance, the tubercle bacilli responsible for reactivated disease often cannot be influenced by further treatment with the agents to which they are no longer sensitive. Such infections are of more than ordinary public health importance, for patients newly infected with these organisms probably will not benefit from treatment with the drugs to which their tubercle bacilli are resistant. Fortunately, this seems not yet to be a serious problem, but the implications for future generations of tuberculous patients are obvious, and emphasize the need for new and better antimicrobial agents for use in treatment.

It is the clinician's responsibility in the diagnosis of tuberculosis to assemble and correlate all available information, and to be certain that for their special studies his laboratory colleagues are provided with adequate and meaningful material. If the data available do not fit into a pattern of diagnosis, he must inquire further. Was the tuberculin test complete? Was the reaction negative because of an immunologic disturbance? Are the roentgenograms adequate? Should further material be sent to the laboratory? Are the mycobacteria demonstrated by smear and culture of the human type? Have they failed to produce disease in guinea pigs because of resistance to isoniazid? Are the patient's tubercle bacilli so few in number that the bacteriologist should be consulted regarding special technics for their isolation?

## MEETINGS *and Postgraduate Courses*

THE CHILDREN'S HOSPITAL OF PHILADELPHIA: (1) Refresher course in pediatric advances for pediatricians and general practitioners, May 28-June 1, conducted by the staff of the Children's Hospital in collaboration with the Department of Pediatrics of the University of Pennsylvania and the Camden Municipal Hospital. Tuition is $100.00. (2) Practical pediatric hematology, June 4-6, conducted by Dr. Irving J. Wolman and other members of the Hematology Department of the Children's Hospital, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition is $60.00. (3) Blood group incompatibilities and erythroblastosis fetalis, June 7-8, conducted by Dr. Thomas R. Boggs, Jr., of the Philadelphia Serum Exchange of the Children's Hospital, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition is $50.00. Additional information may be obtained by writing to Dr. Irving J. Wolman, Children's Hospital of Philadelphia, Philadelphia 46.

UNIVERSITY OF MINNESOTA, MINNEAPOLIS: Continuation course in dermatology for general physicians, June 4-6, at the Center for Continuation Study.

CLINICAL STUDY

# Effects of L-Glutavite® Compared With Metrazol® and Vitamins on Aged Female Psychotic Patients

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ONE of the complications that hinders the progress of medicine toward increasing the longevity of man is the increasing incidence of aged people with nervous or mental disorders. Currently more than one-third of the patients in hospitals for the chronically ill are over 65; the problem of treating the hospitalized aged is one of the country's first challenges.

A number of medications have been utilized in elderly patients to forestall or delay the deteriorating process or to improve various social maladjustments. These medications help patients to become better citizens in the hospital milieu and in some instances permit their discharge.

METRAZOL®, which is known to stimulate brain tissue, has been tried by a number of workers whose reports on its use are conflicting.[1-8] Vitamins, particularly nicotinic acid derivatives, also have been used because of their cerebral vasodilating effect.

PAUL BARRABEE

JAMES H. WINGATE

L-GLUTAVITE®, which contains

| | |
|---|---|
| Monosodium L-glutamate | 3.48 gm. |
| Niacin | 45 mg. |
| Thiamine mononitrate | 0.6 mg. |
| Riboflavin | 0.8 mg. |
| Ascorbic acid | 30 mg. |
| Ferrous sulfate | 11 mg. |
| Dicalcium phosphate | 910 mg. |

has been recommended as an aid in treating

*Dr. Barrabee's work in developing the social environment of the ward was financed by a fellowship grant from the National Institutes of Health.

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L-Glutavite was supplied by Gray Pharmaceutical Co., Inc., Newton, Massachusetts.

senile psychotic patients. The rationale for L-Glutavite is perhaps better at the chemical level than some other compounds.[9,10] Monosodium L-glutamate is effectively absorbed into the blood stream after ingestion and appears in the circulation as glutamic acid. Glutamic acid appears to be the only amino acid which is oxidized in the brain.

BERNARD D. PHILLIPS

MILTON GREENBLATT

There are three ways suggested in which L-Glutavite may be of help: (1) enhancement of cerebral tissue metabolism brought about by an optimal supply of glutamic acid, (2) enhancement of enzymatic oxidations brought about by an optimal supply of riboflavin, thiamine and ascorbic acid, and (3) enhancement of effective vascular flow brought about by the vasodilating influence of niacin aided by the hematinic action of ferrous iron.

The following is a report of the relative effects of L-Glutavite compared with Metrazol and vitamins on aged female psychotic patients.

### *Method and Procedure*

A ward of aged female psychotic patients at the Metropolitan State Hospital in Waltham, Massachusetts, was selected for the purpose of investigating the effect of L-Glutavite, vitamins and Metrazol on the social adjustment and mental status of the patients. There were three test groups composed of 10 patients each. Group 1 was given three packs of L-Glutavite daily. Group 2 received 4½ gr. of Metrazol three times a day. Group 3 took a compound of vitamins that corresponded in quantity and nature with those vitamins which are included in L-Glutavite. All three groups received their medication in tomato juice.

### *The Total Test Group*

These 30 patients were over 65 years old with an average age of 75.5 years. Three-fourths of them were diagnosed as having a chronic brain syndrome with cerebral arteriosclerosis. The remainder had a diagnosis of senile psychosis. The average length of hospitalization was two years. None of the patients had a history of previous mental illness, although in five cases there was positive family history of mental illness. For most of the patients, the illness had occurred rapidly, with psychotic symptoms manifest less than two years prior to the time of commitment.

The total group was almost evenly divided between Protestants and Catholics. About half were native Americans and the balance was evenly divided between those of Canadian and Irish backgrounds. Ten were single, five married, one divorced and 14 widowed. Five of the 30 came from the middle or lower middle socioeconomic level while 25 came from the lower level.

### *Test Subgroups*

Each of the three test subgroups was similar to the over-all group with respect to diagnostic types, average length of stay in the hospital, religion, ethnic origin, and socioeconomic level, and they were also comparable with one another. They did differ somewhat in average age and marital status.

Group 1 had an average age of 78.3 with only one patient in the 60s. Half of group 2 were in their 60s, and the group average age was 70.9. All the patients in group 3 were over 70 with an average age of 77.4.

Regarding marital status, group 1 had only one patient each in the single, married and divorced categories, leaving seven who were widowed. Groups 2 and 3 had no divorced patients. Group 2 had five single, two married and three widowed patients, while group 3 had four single, two married and four widowed.

### *Procedure*

Several weeks before beginning the administration of the medication, the subjects were

closely observed by the authors, attendants, nurses and student nurses who were assigned to the ward. An assessment was then made of the social adjustment and mental status of each patient.

The social adjustment evaluation of patients was the consensus of all the ward personnel as determined by the Barrabee-Hyde Hospital Social Adjustment Scale. This test uses hospital norms as a basis for evaluation in the areas of self-care, cooperation, productivity and sociability. Social adjustment is expressed as a position on a five-point scale representing increasing degrees of deviation from the norms in regard to the individual behavioral items that compose each of the four major areas. Scores range from 5.0 (very satisfactory) to 1.0 (very unsatisfactory). The pre-test evaluations plus detailed behavioral descriptions of each patient by the student nurses made up the behavioral base line for each patient.

The mental status of each patient was assessed by Dr. Wingate after a personal interview. He used a specially prepared scale that was based on the standard procedure for obtaining mental status in current use at the Metropolitan State Hospital. This deals primarily with intellectual functions, thought content, mood and affect.

After the social adjustment and mental status ratings for each patient had been ascertained, medication was begun. Any patient on the ward who wished it, even though not in the test groups, could have tomato juice. It was felt this would reduce any feeling of discrimination between those in and out of the test groups. It was not generally known which patients were in the several test groups.

The medication was continued daily for three months, with little resistance from the patients. At first some of the patients experienced a flushing reaction to the L-Glutavite and to the vitamins. Accordingly, the dosage was reduced by one-half for one week and was then restored to the original with no recurrence of the flushing.

During this three month period, a concerted effort was made to improve the physical appearance of the ward; walls were painted, pictures hung, and new furniture acquired. In addition, a program of social activation was instituted and supervised by Dr. Barrabee. This included the use of volunteers for ward parties, therapeutist for regular occupational therapy activities, assignment of six student nurses as supplementary personnel for these activities, and of four attendants with obligations limited to this ward. Regular meetings with volunteers, attendants and student nurses were instituted to discuss and co-ordinate the program. At the end of the three month period, another evaluation was made of the social adjustment and mental status of each patient in the test groups.

### *Statistical Procedure**

Since reported findings seemed to indicate that Metrazol has had a beneficial effect on the social adjustment and mental status of aged psychotics, one test group was given this drug to determine its effect relative to that of L-Glutavite. The third group, which received vitamins, was considered to be a control group. Since the pre-test and post-test statuses were compared for each subject, the subjects also served as their own controls.

The design of the study and the construction of the rating scales favored the use of nonparametric statistics as described by Moses,[11] Wilcoxon,[12] and Dixon and Massey.[13] The Wilcoxon "T" for matched pairs was employed to test the "null" hypothesis of difference between the pre-test and post-test ratings of all the patients for all scale items, with the notable exception of the item concerned with lability. The analysis of lability consisted of the use of chi-square and the Fisher Exact Method in order to test the hypothesis of independence of drugs and rating change.

The groups were compared as to relative rating differences by use of the Wilcoxon "T" and the Mann-Whitney "H" test, which is a modification of the analysis of variance specifically applicable to nonparametric data. Thus the determination of the relative effects of the drugs was made possible.

Finally, in order to test the possible rela-

*The statistical analysis was done by Carson C. Johnson, Jr., M.S.

tivity of outstanding changes in ratings, the Spearman Rank Correlation Coefficient was computed for certain relationships of categories and of rating changes in categories.

### *Results*

The entire sample of 30 patients showed a post-test change in its ratings from its pre-test ratings in the direction of improvement in both the over-all social adjustment and the over-all mental status. These changes were found to be statistically significant at the 0.001 level. Further analysis revealed that significant rating changes also occurred in the total sample in all the categories of social adjustment: self-care ($P<0.05$); cooperation ($P<0.05$); productivity ($P<0.001$); and sociability ($P<0.001$); and in three of the categories of mental status: thought content ($P<0.001$); mood ($P<0.01$); and affect ($P<0.01$). Only in intellectual functions was there no significant change in the ratings of the total sample's behavior (tables 1 and 2).

Group 1 (L-Glutavite) made significant improvement in the most categories, i.e., over-all social adjustment, self-care, productivity, sociability, over-all mental status, thought content, mood and affect.

Group 2 (Metrazol) made significant improvement in the fewest categories. This occurred in over-all social adjustment, sociability, over-all mental status and thought content.

Group 3 (vitamins) showed significant changes in ratings in the direction of improvement in over-all social adjustment, sociability, over-all mental status, thought content, mood and affect (tables 1 and 2).

Although there were significant changes toward improvement in all three test groups, it is important to note that there were statistically significant differences in the amount of these changes among the groups. In this respect, group 1 (L-Glutavite) showed the most favorable picture, followed by group 3 (vitamins) and group 2 (Metrazol) in that order (table 3).

TABLE 1

IMPROVEMENT IN SOCIAL ADJUSTMENT

| CATEGORY | L-GLUTAVITE *Group 1* | METRAZOL *Group 2* | VITAMINS *Group 3* | *All Groups* |
|---|---|---|---|---|
| Total social adjustment | + | + | + | + |
| Self-care | + | 0 | 0 | + |
| Sleeping | + | 0 | 0 | |
| Eating | + | 0 | 0 | |
| Appearance | 0 | 0 | 0 | |
| Dressing | 0 | 0 | 0 | |
| Cooperation | 0 | 0 | 0 | + |
| Routine | 0 | 0 | 0 | |
| Ward work | 0 | 0 | 0 | |
| Productivity | + | 0 | 0 | + |
| Occupational therapy | + | 0 | 0 | |
| Ward work | 0 | 0 | 0 | |
| Sociability | + | + | + | + |
| Verbal interaction | + | + | + | |
| Group participation | + | 0 | 0 | |
| Solidarity | 0 | 0 | + | |

+ means significant improvement

0 means no significant improvement

Group 1 shows significant improvement in three categories and five items
Group 2 shows significant improvement in one category and one item
Group 3 shows significant improvement in one category and two items

All groups show significant improvement in total social adjustment

TABLE 2

IMPROVEMENT IN MENTAL STATUS

| CATEGORY | L-GLUTAVITE *Group 1* | METRAZOL *Group 2* | VITAMINS *Group 3* | *All Groups* |
|---|---|---|---|---|
| Total mental status (not including intellectual functions) | + | + | + | + |
| Intellectual functions | 0 | 0 | 0 | 0 |
| Orientation | 0 | 0 | 0 | |
| Ability to abstract | 0 | 0 | 0 | |
| Remote memory | 0 | 0 | 0 | |
| Recent memory | 0 | 0 | 0 | |
| Thought content | + | + | + | + |
| Preoccupation with past | + | 0 | 0 | |
| Preoccupation with present | + | + | + | |
| Plans for future | 0 | 0 | 0 | |
| Somatic complaints | + | 0 | + | |
| Hallucinations or delusions | 0 | 0 | + | |
| Mood | + | 0 | + | + |
| Elevated | 0 | 0 | 0 | |
| Depressed | 0 | 0 | 0 | |
| Apathetic | + | 0 | 0 | |
| Labile | 0 | 0 | + | |
| Affect | + | 0 | + | + |
| Spontaneous | + | 0 | 0 | |
| Reacts only when approached | + | 0 | + | |
| Listless, withdrawn | 0 | 0 | 0 | |
| Rejects approaches | + | 0 | 0 | |

+ means significant improvement

0 means no significant improvement

Group 1 shows significant improvement in three categories and seven items
Group 2 shows significant improvement in one category and one item
Group 3 shows significant improvement in three categories and five items

All groups showed significant improvement in total mental status not including intellectual functions

The degree of improvement in group 1 was significantly greater than that of group 2 in over-all social adjustment, self-care, sociability, over-all mental status, thought content and affect. It was significantly greater than group 3 in over-all social adjustment and self-care.

Group 3 showed a greater change toward improvement that differed significantly from that of group 2 in thought content only. In no instance was there a significant difference in amount of change in favor of group 3 over group 1, or of group 2 over the other groups.

The different scores of the total sample in over-all social adjustment and over-all mental status showed no correlation. However, they did show a significant correlation, +0.41, for group 2. (This should be regarded with caution due to the failure of the total sample to show a correlation.) The over-all social adjustment change scores were related significantly to increasing age for the total sample, +0.42, and for group 2, +0.60. This was also true for the total sample, +0.37, but the test groups individually failed to show such a correlation with any significance. The only other correlations were both shown by group 1: change in sleeping with change in eating, +0.74, and change in productivity with change of mood, +0.84. Furthermore, no relationship was found between marital status and a significant change.

### *Discussion*

It is now generally accepted that when psychotic patients are offered a program of ward betterment and social activation, they usually

TABLE 3

DIFFERENCES OF IMPROVEMENT AMONG GROUPS

| CATEGORY | GROUPS | SIGNIFICANCE |
|---|---|---|
| Over-all social adjustment | *1 and 2 | + |
| | *1 and 3 | + |
| | 2 and 3* | 0 |
| Self-care | *1 and 2 | + |
| | *1 and 3 | + |
| | 2 and 3* | 0 |
| Cooperation | *1 and 2 | 0 |
| | 1 and 3* | 0 |
| | 2 and 3* | 0 |
| Productivity | *1 and 2 | 0 |
| | *1 and 3 | 0 |
| | 2 and 3* | 0 |
| Sociability | *1 and 2 | + |
| | *1 and 3 | 0 |
| | 2 and 3* | 0 |
| Over-all mental status (not including intellectual function) | *1 and 2 | + |
| | *1 and 3 | 0 |
| | 2 and 3* | 0 |
| Thought content | *1 and 2 | + |
| | *1 and 3 | 0 |
| | 2 and 3* | + |
| Mood | *1 and 2 | 0 |
| | *1 and 3 | 0 |
| | 2 and 3* | 0 |
| Affect | *1 and 2 | + |
| | *1 and 3 | 0 |
| | 2 and 3* | 0 |

+ means significant difference in improvement

0 means no significant difference in improvement

* denotes the group showing the larger amount of improvement

respond by improvement in their mental and social behavior.

On the assumption that this is also true of aged psychotics, it would be reasonable to believe that the subjects of this study had benefited from the social program to which they had been exposed. Since the total sample did show a significant improvement in social adjustment and mental status, the question then arises as to how much, if any, of this improvement was due to the various medications.

It is virtually impossible to know to what extent the improvements noted were influenced either by the social program or by the medications. Nevertheless, the results do indicate that the medications produced an effect on the social adjustment and mental status of the test patients, in addition to the influence of the social program.

The justification for this statement is based on the significant differential results between the test groups which, in turn, are also pertinent to the comparative effectiveness of the medications. To put it in another way, if the medications had no effect or if they had the identical effect, it is unlikely that there would be a significant difference in the kind and amount of improvement among the groups. Furthermore, in the former instance, improvement presumably would then be attributable to the social program alone. In the latter instance, the social program would share, in some unknown degree, with the medications the responsibility for the improvement.

Since there actually were significant differential results among test groups, it would appear that not only did the medications influence the changes in mental and social behavior, but also that there were differences in the comparative effect of the medications in this respect. However, because it is still unknown what part was played by the social program, which certainly must have made some contribution, the results must be interpreted with the social program as a necessary concomitant to the environmental setting. In other words, the differential effects which seem to be attributable to the medications must be viewed as taking place in conjunction with the rather extensive social program that accompanied the administration of the medications.

Despite this, however, the consistently low correlations add confidence to the conclusion that changes in mental and social behavior were dependent on the medications. It seems quite clear that little or no "halo" effect surrounded the ratings of the individual subjects. Also it may be concluded that the improvement in the various categories was liberally spread among all the subjects and no individual subjects were particularly superior in the amount of improvement.

The small size of the sample is another

qualifying restriction on the interpretation of the results of this study. For the purpose of statistical tests of significance, the sample size was close to the minimum that could afford any reliable statistical manipulation. Accordingly, the study must be realistically viewed as a pilot effort, with the findings important primarily as indicating trends which must be validated by more extensive research.

Keeping in mind the provisions noted, it then can be stated that the findings of this study present strong evidence that the administration of L-Glutavite and vitamins, and possibly Metrazol, to aged female hospitalized psychotics led to a change in their mental and social behavior that can definitely be interpreted as improvement. Meaningful improvement was accomplished throughout the entire sample of 30 subjects. However, the effect of L-Glutavite seems to be the most outstanding on the basis that the group receiving L-Glutavite showed improvement in more categories and items than either of the other two groups. and the amount of improvement was significantly greater than the Metrazol group in over-all social adjustment, self-care, sociability, over-all mental status, thought content and affect, and significantly greater than the vitamin group in social adjustment and self-care.

The group receiving vitamins showed the next best results. Although there were no categories in which the amount of improvement of these subjects was significantly greater than those receiving L-Glutavite, the vitamin group did show a significantly greater amount of improvement than the Metrazol group in thought content as well as showing improvement in more categories and items than those receiving Metrazol.

The Metrazol group gave least evidence of change in the direction of improvement. Because there was no other test group that showed significantly less improvement, it is impossible to know whether or not the improvement observed in this group was due in any significant degree to the administration of the drug rather than to the social program.

### *Summary*


1. Thirty aged female psychotic patients at Metropolitan State Hospital, Waltham, Massachusetts, in three test subgroups of 10 each, were given L-Glutavite, Metrazol and vitamins, respectively, for a three month period. Mental and social behavior were rated before and after administering the drugs by a revised Barrabee-Hyde Hospital Social Adjustment Scale and a special mental status scale.

2. All subjects showed significant improvement in mental and social behavior.

3. Greatest improvement occurred in sociability, productivity and thought content. Less outstanding were improvements in self-care, cooperation, affect and mood.

4. The L-Glutavite group improved—and in significantly greater amounts in several instances—in more categories and items than did either of the other two groups.

5. Vitamins also influenced improvement but less markedly in scope and amount than L-Glutavite, although more so than Metrazol.

6. The Metrazol group showed least significant improvement, and it is questionable that Metrazol influenced the improvements noted.


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We are grateful for the cooperation and assistance of Dr. William McLaughlin, Superintendent of the Metropolitan State Hospital, and Dr. Myer Asekoff, Clinical Director of the Metropolitan State Hospital.

*SCIENTIFIC EXHIBIT*

# Improved Adrenal Denervation for Essential Hypertension

SHERMAN A. EGER*

*The Jefferson Medical College, Philadelphia*

This exhibit introduces an improved method of adrenal denervation and shows the results effected by the procedure in 10 cases of essential hypertension which were followed closely for from one to four years.

The 20 or more sympathetic nerve filaments supplying each adrenal gland come from so many different and widely separated sources that severing them at the adrenal capsule is the only way to assure complete denervation (figure 1).

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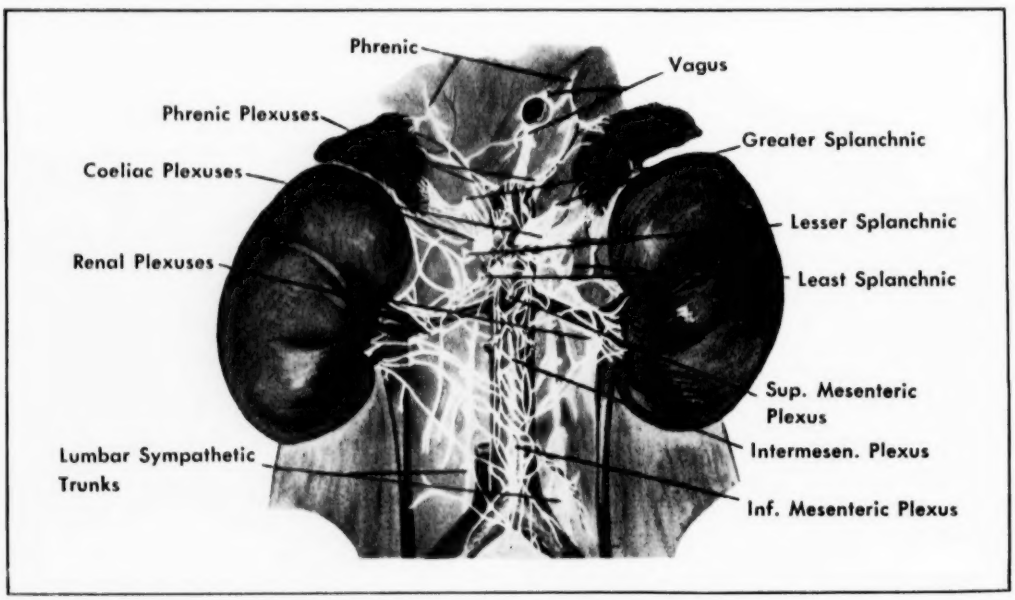



FIGURE 1. Nerve supply of adrenal glands.

## INDICATION and CONTRAINDICATION to OPERATION

The indication for adrenal denervation in cases of essential hypertension is the predominance of a neurogenic element, with little or no evidence of other causative factors. The degree of neurogenic element present can be determined best by sodium AMYTAL® test (sleep test) performed as follows:

Sodium Amytal, 3 gr., is administered orally, and the dose is repeated at one hour intervals until the patient cannot be awakened by such external stimuli as shaking or calling him by name. No patient in the study required more than three doses, or 9 gr.

The degree to which the blood pressure falls during the test determines the effect denervation of the adrenal glands will have. A fall to a normal level (below 150 systolic and 100 diastolic) is ideal and means that the neurogenic element is predominant. If, however, the blood pressure remains above normal levels, it means that other factors, chiefly renal, are responsible and must be evaluated.

Adrenal denervation is contraindicated in cases of essential hypertension when the fall in blood pressure during the sodium Amytal test is insufficient to influence favorably the present state and future course of the hypertension.

## OPERATIVE TECHNIC

The operative procedure consists of surrounding each completely denervated adrenal gland with a 1 in. thick layer of OXYCEL® (oxidized cellulose) which, although absorbable, causes the formation of a fibrous tissue encasement averaging ½ in. in thickness which completely encircles the adrenal glands. This fibrous tissue acts as an impenetrable barrier to the regenerating nerves and makes the changes produced in the adrenals by denervation permanent.

*Anesthesia*—Ether should be administered intratracheally to insure a plentiful supply of oxygen, to provide positive pressure if the pleura is punctured, to avoid changes in blood pressure, and to eliminate psychic trauma.

*Position*—The patient should lie fully on his side, with his twelfth rib as an apex to "break the table" at about 20 degrees.

All instruments used should be at least 8 in. long. Care should be taken to avoid injury to the central veins which may result in thrombosis and necrosis. The adrenal glands are friable and easily damaged and should not be grasped during dissection.

The operation should take about one hour. Patients are permitted out of bed on the second or third postoperative day, and are discharged from the hospital in 10 to 14 days. A four to six week interval must be allowed before denervating the second adrenal gland, so that the first has had time to recover from any operative trauma.

FIGURE 2. A 5 in. incision is made parallel to and 1 in. below the twelfth rib.

FIGURE 3. When the kidney is rotated medially, the lower edge of the adrenal gland appears. Note that the nerve being held tautly with the forceps sends several branches into the adrenal gland. All nerves are severed close to the adrenal gland.

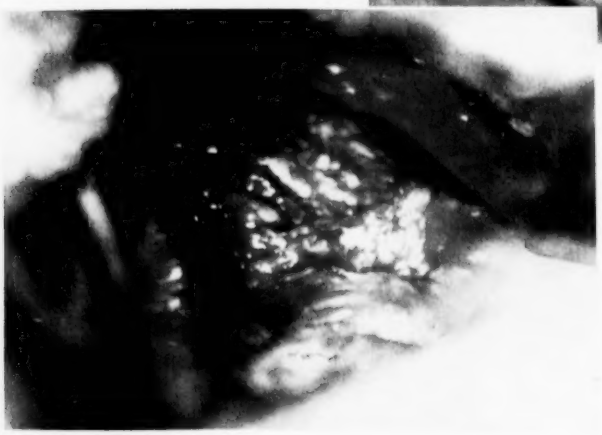


FIGURE 4. Denervation is continued along the anterior and medial surfaces; nerves that are near the central vein are severed last, when all sides can be seen.

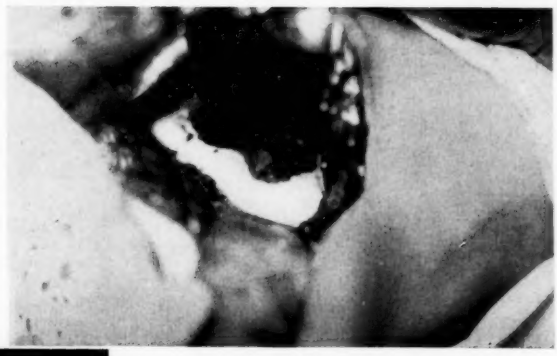


FIGURE 5. The adrenal gland, after denervation of all surfaces has been completed and the Oxycel placement around the gland is almost completed.

FIGURE 6. Oxycel placement has been completed.

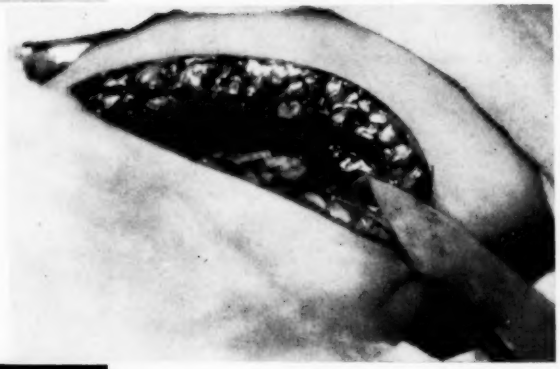


FIGURE 7. The drain is inserted and the kidney is returned to its normal position.

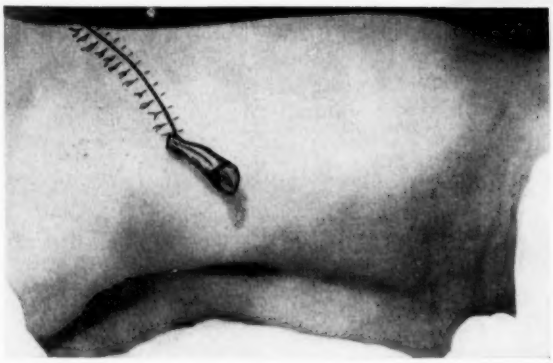
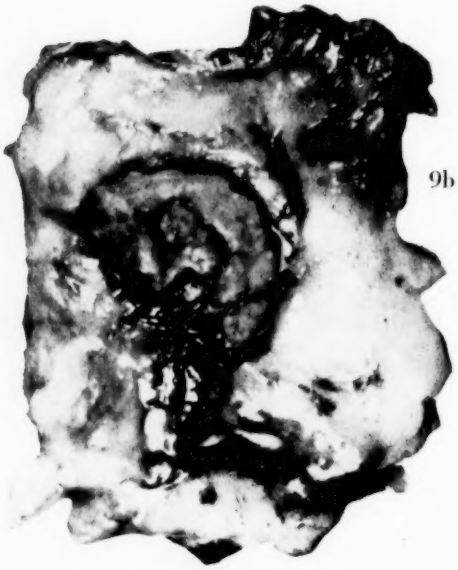


FIGURE 8. Operation is completed. The drain is removed in one week.

(See legends for figures 9-16)

Changes produced around the adrenal glands by Oxycel (x 20)

9a



9b

FIGURE 9. Autopsy performed two years after operation on the adrenal glands shows that the Oxycel has been replaced by dense fibrous tissue, which forms a thick impenetrable barrier to regenerating nerves. (The top portions of both specimens have been dissected upward to expose the adrenal glands in the center of each mass.)

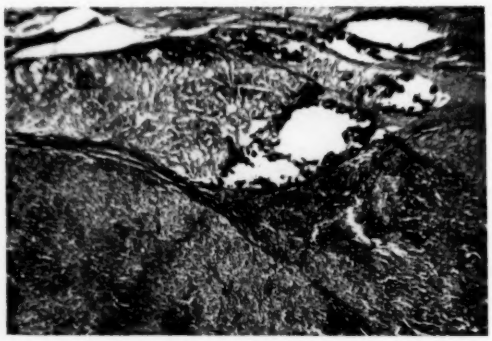
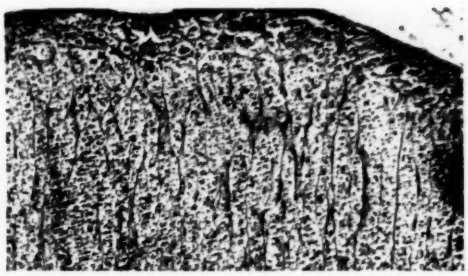


FIGURE 10. The adrenal capsule across the middle of the picture demarcates the Oxycel-produced fibrous tissue barrier above from the adrenal cortex below.

Changes produced in the adrenal cortex by denervation (x 50)

11



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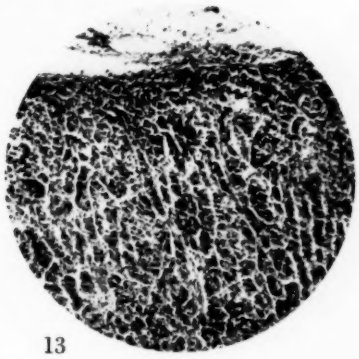

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FIGURE 11. Biopsy specimen of tissue at the time of denervation. The cells are swollen and their characteristic cordlike arrangement is indistinct.

FIGURE 12. Two years after operation, at time of autopsy, the cells are no longer swollen and their cordlike arrangement has become prominent.

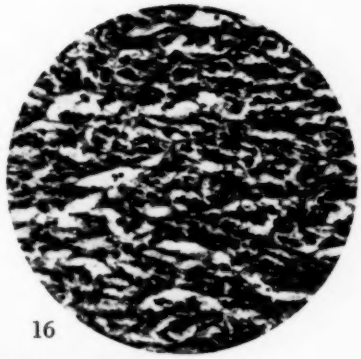
FIGURE 13. Normal cells for comparison.

Changes produced in the adrenal medulla by denervation (x 100)

FIGURE 14. Biopsy specimen taken at the time of denervation shows numerous large cells and *(lower left)* frequently seen nerves.

FIGURE 15. Examination at autopsy two years later disclosed very few large cells and no nerves.

FIGURE 16. Normal adrenal medulla for comparison.



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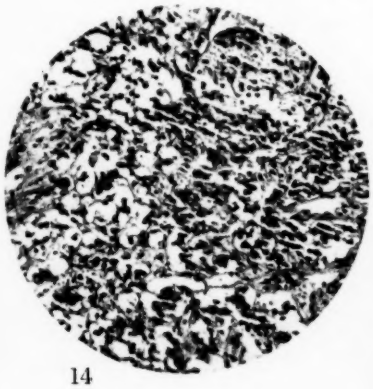

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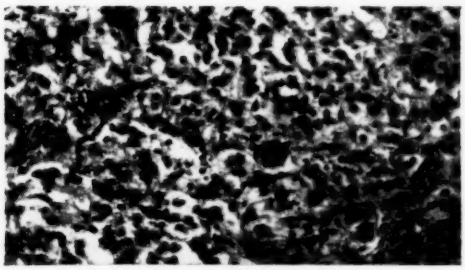

15

CLINICAL DATA

10 Cases of Essential Hypertension Followed One to Four Years After Bilateral Adrenal Denervation

| | Improved (5 cases) | Unimproved (5 cases) |
|---|---|---|
| Age | 39-57 yr. | 37-60 yr. |
| Average | 47 yr. | 47 yr. |
| Sex | | |
| Female | 4 | 4 |
| Male | 1 | 1 |
| Duration of hypertension | 3-10 yr. | 8-14 yr. |
| Average | 8 yr. | 10 yr. |
| Ambulatory blood pressure | 155 175 180 180 200 | 180 220 230 260 320 |
| Average | 105 120 120 120 135 | 130 130 160 165 200 |
| Symptoms | Headache with nervousness | Headache with nervousness |
| Fundi | Grade 2 or less | Grade 2 or more |
| Sodium Amytal test | All became normotensive | None became normotensive |
| Results of operation | | |
| Blood pressure | Remained normal or improved markedly in each case | Never remained significantly lowered |
| Symptomatic improvement | Constant | Not constant |
| Fundi | Usually improved and never worsened | Unchanged |
| Adrenal insufficiency | None | Replacement therapy was indicated in one case |
| Deaths | 0 | 4* |

*1 at 24 hr. due to congestive heart-failure (age 49).
1 at 1½ yr. due to strokes (age 62).
1 at 1½ yr. due to uremia (age 46).
1 at 2 yr. due to strokes (age 47).
All of these patients had advanced hypertension with preoperative organic complications.

# CONCLUSIONS

1. The improved method of bilateral adrenal denervation described is a simple, safe and effective procedure for producing definite and lasting changes in the adrenal glands. These changes are accompanied by a lessening of the neurogenic element in essential hypertension and its symptoms without causing undesirable side effects. It might be said that this method actually removes the tension from hypertension.

2. The best results are obtained in hypertensive patients whose blood pressure readings fall to an unquestionably normal level during the sodium Amytal test. Therefore, it is the degree of neurogenic element present that is important and not the age of the patient or the duration of the hypertension.

3. Operating for advanced hypertension after serious organic complications have developed does about as much good as operating for cancer after it has metastasized.

# CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

***Case Report***

A 25 year old white man was admitted to the hospital May 10, 1954, complaining of a mass in the left side of the neck of two weeks' duration. His family physician had administered antibiotics intramuscularly but the mass had regressed only moderately. A smaller mass had appeared in February 1954 when the patient had a sore throat; it had disappeared with antibiotic therapy.

The left pupil was asymmetric. A 10 cm. mass in the left supraclavicular triangle extended into the sternocleidomastoid muscle. The liver was palpated two fingerbreadths below the right costal margin. The prostate was soft and boggy. Other physical findings were within normal limits.

The red blood cell count was 4,720,000, hemoglobin 14 gm.; white blood cell count 9900 with 72 per cent neutrophils and 28 per cent lymphocytes. Urinalysis and serologic tests gave negative findings. The sedimentation rate of the erythrocytes was 21 mm. Serum calcium was 10.7 mg., serum phosphorus 3.6 mg. The thymol turbidity was 3 units, serum bilirubin 1.2 mg., and the BROMSULPHALEIN® excretion test showed 8 per cent retention. The prolan A was 175 mouse units in 24 hours and a repeat examination showed 160 mouse units in 24 hours. Total protein was 7.6 mg., albumin 4.6 mg., globulin 3.0 mg. and alkaline phosphatase 3.3 Bodansky units.

On May 14, excision biopsy of the neck mass was performed. Microscopic sections showed metastatic adenocarcinoma, primary undetermined, although the slides were interpreted as suggestive of thyroid origin.

Two weeks after admission a mass in the right upper quadrant of the abdomen was first noted. An intravenous pyelogram and upper and lower gastrointestinal series were negative. Bronchoscopy was negative.

On June 3, left hemithyroidectomy and left radical neck dissection were done. Microscopic sections of the specimen did not disclose evidence of tumor. On June 21 the abdomen was explored. Large, fixed retroperitoneal nodes were noted in the periaortic region, extending from behind the pancreas to the aortic bifurcation. Microscopic sections revealed metastatic adenocarcinoma. On July 6, intravenous nitrogen mustard therapy was started and followed by deep x-ray therapy to the abdomen. The patient was discharged on August 24. At follow-up examination in November he was asymptomatic and had gained 8 lb.

He was readmitted December 13, 1954, complaining of pain in the left side of the

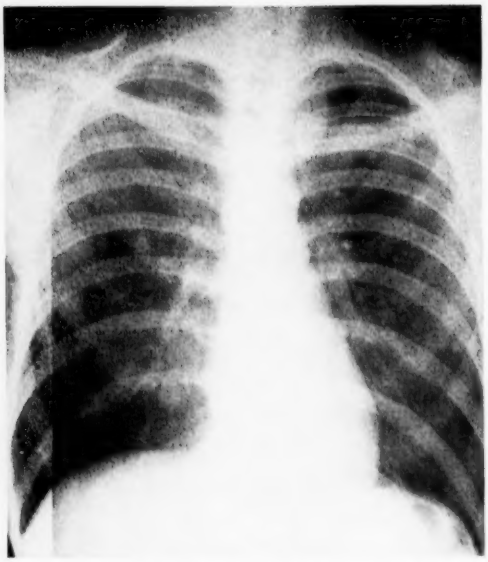

FIGURE 1. Chest x-ray showing multiple bilateral nodular metastases.

abdomen radiating to the back of about one month's duration. He also complained of constipation. There was a mass at the lower end of the neck incision, about 3 to 4 cm. in diameter, and nodes were palpable deep in the left supraclavicular fossa. There was a suspicious mass in the right upper abdominal quadrant. A chest roentgenogram revealed a mass in the left upper mediastinal border extending into the neck.

The red blood cell count was 3,600,000, hemoglobin 11 gm., white blood cell count 5200. Urinalysis disclosed a trace of albumin, and 8 white blood cells and 3 red blood cells per high power field, with an occasional hyaline cast. Alkaline phosphatase was 5.9 Bodansky units. A barium enema did not disclose any abnormality.

Aspiration biopsy of the neck mass revealed malignant cells, and the region was treated with deep x-ray. A retrograde pyelogram on January 17, 1955 was interpreted as suggesting a space-occupying lesion in the left kidney.

While the patient was on pass, he suddenly became ill and was hospitalized at a local hospital. After two weeks he was transferred to Hines. A chest x-ray revealed multiple bilateral nodular masses consistent with metastases (figure 1). On March 14, emesia of a large amount of coffee-ground material occurred. The patient died March 16, 1955.

### *Discussion*

DR. LLOYD: There are a few things in the physical examination and in the history that were omitted, possibly intentionally, and that one would like to know about. However, this man had a thorough medical work-up, he was seen by the urologic department, the genitourinary tract was studied, and he also had a laparotomy. Despite all this exploration and study, the diagnosis was not made or the primary focus of the metastatic lesions determined until autopsy, if then. I suspect that this is one of those cases in which either the postmortem examination will provide the diagnosis or we will be unable to make one. I personally feel that in these situations it is no disgrace to be unable to make a diagnosis. There are diagnoses which can be made only from certain physical findings or aspects of the history, diagnoses which cannot otherwise be made. Unfortunately, there are also situations where the final diagnostic evidence is destroyed because of an incorrectly performed autopsy or an inadequate pathologic study—the tissues overlooked, destroyed or altered. These cases require extremely careful study. The pathologist must know the clinical history and understand the clinical picture completely before he does the postmortem examination.

The patient's age, 25 years, narrows down to a certain extent the things we might expect to find. He obviously had metastatic adenocarcinoma in the supraclavicular triangle. He also had metastatic carcinoma to the retroperitoneal nodes, and I suspect he probably had metastatic adenocarcinoma in the liver, although this was not clear. I suspect further, from the pupillary asymmetry, that he might possibly have had a metastasis in the brain. We also must consider the histopathologic resemblance of the neck tumor to a thyroid carcinoma; this may or may not have significance but we must keep it in mind.

Since I was asked to discuss this case, ob-

FIGURE 2. Papillary adenocarcinoma, original mass in left side of neck.

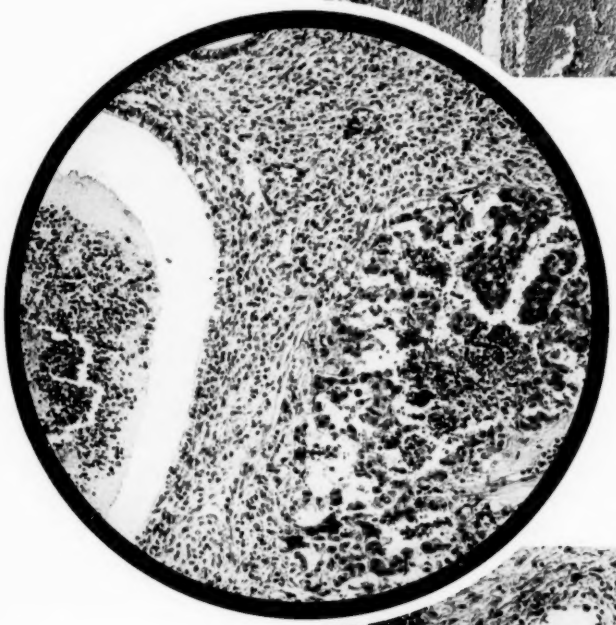

FIGURE 3. Areas of papillary carcinoma and cystic glandular areas lined by cuboidal and columnar epithelium. The glandular lumen is filled with secretion resembling thyroid colloid.

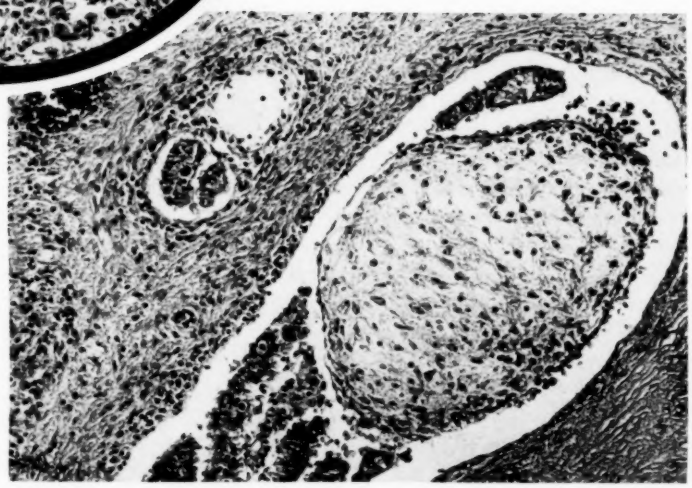

FIGURE 4. Two types of tissue in mass in neck. Intravascular invasion of papillary adenocarcinoma and sarcomatous stroma.

viously there is some tie-in with the genitourinary system despite the initially negative findings in this respect. Even though examinations of the urinary tract may be done very accurately, we are sometimes a bit careless about them. Pyelographic and urinary studies frequently give a lot of information, but sometimes early pathology is not discovered because of improperly associated physical examination. Early tumors of the kidney may not be discovered on pyelography.

Laparotomy was performed after the mass had been removed from the neck, and all the lymph nodes were visualized, from the celiac axis down to the bifurcation. I would like to ask, hypothetically, how thoroughly were these nodes visualized? Were they merely palpated? How large were they? Were they greatly enlarged, and, if so, where was most of the enlargement? Was it high up, near the celiac axis, or scattered evenly down along the entire length of the aorta and the vena cava? I realize it is difficult, in a transperitoneal laparotomy, to check on these nodes. The best way to see them is retroperitoneally after stripping the peritoneal contents over to the side.

The protocol states that the gallbladder was not visualized, and that a definite cause for the abdominal mass could not be determined. A biopsy specimen removed from the area behind the pancreas was interpreted as metastatic adenocarcinoma. The kidneys and adrenals were normal to palpation. It is very possible, even when pathology is present, to palpate the kidneys and adrenals transperitoneally and not find anything. A thorough exploration of the kidney is not possible, and tumors around the papillae and deeper in the renal substance may very easily be missed, unless the kidney is freed and stripped and examined under complete vision; even then, tumors can be overlooked.

On rectal examination the prostate was soft. The alkaline phosphatase of the serum is mentioned, but the acid phosphatase is not.

A very significant omission here is reference to the testicles. What did scrotal palpation show? Were both testicles in the scrotum, or was one missing? That is very important. I have seen cases where a thorough urinary tract examination was made and no one took the trouble to do a careful scrotal palpation, and the testicle was retained in the abdomen and was the site of a primary tumor.

As to the broad possibilities in this case, I shall start at the very bottom. From the retroperitoneal and supraclavicular distribution of the metastases, in a 25 year old patient, my first vote would be for a testicular tumor with generalized metastases, the primary tumor probably overlooked—either a small tumor or one that was retained either in the inguinal canal or, more likely, in the abdomen, overlooked on examination and probably also on exploration; this can very readily be done.

Metastases similar to these can also occur with adenocarcinoma from the prostate. The fact that the prostate was soft on rectal examination makes this improbable, although soft carcinomas of the prostate can occur and cause extensive metastases; these, however, are extremely rare. Adenocarcinoma can occur in the bladder and metastasize in the way the lesions were noted in this case, but, again, this tumor is exceedingly rare. I think at Hines we have had a total of 16 or 17 such cases.

I wonder about this mass beneath the right rectus muscle, which could be a carcinoma of the urachus. Was the exploratory laparotomy incision made in the midline? If so, that lesion certainly would have been picked up. Usually the lymph node distribution with carcinoma of the urachus is a bit different from that found here.

The next possibility, and this is a definite one, is adenocarcinoma of the kidney. We might also consider a retroperitoneal tumor, a misplaced rest, or a misplaced rest on the nature of a Brunn's tumor. The large mass which was palpated retroperitoneally on the left side and which was thought to be possibly a hypernephroma could still be a metastasis to retroperitoneal nodes. It could be a retroperitoneal tumor metastasis from a carcinoma.

I would summarize the entire situation as follows. I frankly and honestly cannot make the diagnosis here from the findings as they are presented. However, I would give my first vote to carcinoma of the testicle with metastases, because of the distribution of the me-

tastases and because of the patient's age. Prostatic carcinoma is unlikely in a 25 year old; adenocarcinoma of the bladder is very unlikely. Carcinoma of the urachus is possible—it may even occur in children. Carcinoma of the kidney is possible but unlikely at that age; the same goes for retroperitoneal carcinoma. This has been a very interesting case. I feel it represents a testicular tumor with retroperitoneal and pulmonary metastases.

### *Postmortem Examination*

DR. R. R. SCHREK (PATHOLOGIST): In these cases of obscure primary carcinoma, the best opportunity for diagnosis is at autopsy. It takes very careful search with a full knowledge of the history sometimes to find the exact primary, and even then it is impossible at times. Microscopic examination may help, and in this case the final recourse for diagnosis was on the basis of the microscopic findings.

Each pleural cavity contained about 250 cc. of yellowish-gray, cloudy fluid, and the lungs were only moderate in size, 450 and 480 gm. A moderate number of nodules were found, as you saw on the x-ray (figure 1), measuring up to 4 cm. in diameter. The important feature of the nodules was that they were reddish and hemorrhagic. The liver had only one metastatic nodule, 8 cm. in diameter, also characterized by considerable hemorrhage and necrosis. There were enlarged lymph nodes all along the aorta, and large retroperitoneal lymph nodes. These masses of tumor seemed to be particularly prominent in the upper abdomen and to largely replace the pancreas. The upper abdominal mass measured 25 by 15 by 10 cm. In view of the considerable replacement of the pancreas, the diagnosis of carcinoma of the pancreas was made at the time of autopsy. This is somewhat inconsistent with the report that at laparotomy the pancreas was not involved, although there were metastatic nodes near the pancreas. The adrenals were small and appeared normal, and did not contain metastatic lesions. The kidneys were normal in size, 150 and 160 gm.. and did not have any tumor nodules. The prostate was moderate in size and the testes were reported to be normal or somewhat smaller than normal, with atrophy, as might be expected in view of the chronic disease. So the gross diagnosis was carcinoma of the pancreas.

The microscopic appearance was not consistent with carcinoma of the pancreas. Some areas reveal large multinuclear, syncytial giant cells associated with Langhan's-type cells. These areas are very hemorrhagic and the total picture strongly suggests choriocarcinoma. Other areas show a papillary carcinomatous growth (figure 2) while still others show dilated and cystic glandular formations lined by well-defined cuboidal or columnar epithelium. Some of the papillary areas strongly resemble papillary adenocarcinoma of the thyroid (figures 3 and 4). There are areas of malignant edematous stroma associated with the epithelial structures. A few areas resemble precartilaginous tissue. The gross and microscopic examination of the testes did not reveal evidence of tumor formation. The microscopic examination suggests that the diagnosis is malignant teratoma with extensive metastases, primary origin undetermined.

# The Function of a Psychosomatic Unit in a General Hospital

JANIS L. BEST, ZACK RUSS, JR. AND EUGENE DAVIDOFF

*Schenectady, New York*

FACILITIES for psychiatric evaluation and therapy within the Ellis Hospital and in this area formerly were inadequate. Although there were a few practicing psychiatrists in the local area, only a minimal number of their patients were admitted to the hospital. Those who were admitted received only supportive therapy, as the more intensive, specific therapeutic psychiatric treatments generally were not feasible.

The advent of the state pilot unit, the Psychosomatic Unit of Ellis Hospital, a psychosomatic unit designed for a general hospital, opened a new avenue for more specific, intensive treatment of emotionally ill individuals. These facilities, including attendance by trained personnel, were made available to patients referred from various community agencies, the emergency room of the hospital, and physicians in the local and surrounding areas. Inpatients of the main hospital were seen in consultation on request of their attending physicians.

Although the unit's primary function was treatment of psychosomatic and neurotic cases, we soon encountered many other types of psychiatric problems. The unit was expected to

JANIS L. BEST

EUGENE DAVIDOFF

carry full responsibility for thorough evaluation, treatment and disposition of the latter as well as of the former. These new cases included the various types of psychosis such as arteriosclerotic, senile, epileptic, alcoholic, schizophrenic, manic-depressive and involutional, and psychoses accompanying other organic diseases—e.g., cardiovascular disease and carcinoma. Also included were many cases of drug toxicity with psychotic reaction (barbiturates, bromides, morphine and derivatives). Other patients without psychoses but in need of specialized attention for emotional difficulty included epileptics, alcoholics, chil-

dren with behavior problems, and mentally deficient persons. Consequently, what started as a controlled project limited to psychosomatic cases soon extended in an attempt to cope with the many new problems. This has been done on both an inpatient and an outpatient basis.

A psychosomatic unit in a general hospital stresses treatment in the community rather than removal of the patient from the community. Heretofore the attitude of the average person in the community has been that psychiatrists treat only wealthy persons who can afford expensive hospitalization, or severely disturbed persons who require removal from the community because of their erratic behavior or who are indigent. Not having competent consultation facilities available to offer advice in handling emotional disturbances, family physicians have been unable to interpret to patients or their families how much they can expect to gain from psychiatric treatment, even though the disorder is recognized early.

A general hospital, located in and serving a community, provides an ideal setup for treating early-recognized and milder forms of emotional disturbances, as it offers adequate facilities for study and maintains the relationship between patient and family physician as well as among patient, family and community. The general hospital should not be expected to serve as a place for custodial care of patients requiring long-term treatment or of those with irreversible processes which progress steadily downhill. Neither should the general hospital be expected to maintain maximum security for severely disturbed patients, although it may function as a place for brief observation prior to disposition of such cases.

In 1949, the administrators of the Ellis Hospital of Schenectady recognized the community's need for psychiatric facilities. At that time the only available agencies offering such facilities were another general hospital 15 miles away, a private licensed institution which offered only custodial care, and the state hospital serving the district, 85 miles distant. The original plan called for a unit which would function as an open unit, with a capacity of 20 patients, for care and treatment of milder neurotic disturbances, mostly patients with psychosomatic complaints. Two more secure rooms were to be available for temporary detention of psychotic, more severely disturbed patients before transfer to other facilities. Consultation and diagnostic services were to be offered to other physicians in the hospital and in the community, and to other recognized social agencies. A training program for postgraduate study was designed for teaching other physicians interested in psychiatry.

However, as the physicians and the community have become aware of the services offered by the unit and its ability to fulfill a great need as a well-run psychiatric facility, the demands have increased and the area it serves has expanded. The local courts were in need of competent medical advice in some of their cases and were one of the first social agencies to look to the unit for psychiatric evaluation. The local school system sought help in handling problem children. Ministers welcomed a source of medical advice regarding emotionally disturbed parishioners. Other social agencies in this and other communities in the area sought the psychiatric evaluation and guidance available. Industrial concerns sought help regarding the advisability of hiring men with histories of emotional disturbances, or placement, on return to work, of employees who had been hospitalized for emotional disorders.

The physicians of the community and of the area continue to make the greatest demand on the unit's facilities. Patients are accepted only on referral from their physician or from a recognized social agency. The family physician welcomes the opportunity for consultation with specialized knowledge. He also utilizes the technical equipment and personnel, such as the electro-encephalogram and its interpretation, and psychologists. More and more often, he seeks aid in the hospital management of his patients—advice as to advisability of operation or type or amount of sedation, and aid in diagnosis of emotional or neurologic disorders or both. Temporary care, on the psychosomatic unit, of emotionally disturbed or delirious patients admitted

to other services in the hospital precludes their transfer to distant psychiatric institutions and makes for better public relations.

The community becomes aware of the existence of such a unit and makes a clamor for further information about it and seeks further service. School and church groups, civic organizations and other social and welfare groups request that the personnel come and enlighten them about the type of work carried on. This community education is a vital part of the functioning of a unit set up to serve the needs of the people. One of the greatest demands is made by persons who are interested in children, as they feel that preventive measures taken now will mean much more happiness in later years and perhaps prevent severe maladjustments in the future. This community project, in turn, makes for greater demand by these agencies, and the family physicians, for evaluation and treatment of children. At this time there is no agency in the area devoted exclusively to treatment of children, and the unit at Ellis Hospital has responded by offering psychiatric evaluation and treatment of children.

### *Outpatient Service*

An integral part of any psychiatric facility is a well-organized outpatient department. Many physicians request evaluation of their patients on an outpatient basis, with decision as to hospitalization left to the specialist. Many patients are seen who do not require hospitalization, and their emotional problems can be aided by regular consultations. This is of tremendous advantage to them, as they can continue in their own milieu and do not suffer economic loss by prolonged absence from work. Outpatient follow-up for patients previously hospitalized is a necessity for successful treatment of emotional disturbances; social planning, interpretations to families, and maintenance of a positive relationship with the unit all aid the patient who is reorganizing his defenses against anxiety-producing situations by psychotherapeutic interviews.

The outpatient department in its first year had 3,692 scheduled and kept appointments in addition to visits by members of families of hospitalized patients for information and interpretation. During the next 12 months there were 4,433 scheduled and kept appointments. In 1952 there were 5,809 appointments scheduled and kept. The electro-encephalographic department functions as part of the outpatient facility, although it serves hospitalized patients as well; in the first year, 150 electroencephalograms were made; in the second, 328, and in the third, 305.

The staff of this outpatient department at present consists of the following: four physicians (chief psychiatrist, assistant psychiatrist and two residents); four psychiatric social workers (a full-time chief social worker, two part-time social workers and a student psychiatric social worker); four psychologists (two part-time and two consulting); one electro-encephalographic technician; two secretaries; office manager; two stenographers (one full-time and one part-time), and several volunteers from the hospital auxiliary society.

### *Personnel*

The number of personnel necessary to staff such a project depends on the size of the organization, the area it will serve and the number of patients it will handle. At its inception in 1949 the unit had only one physician and no other professionally trained personnel. The bulk of the work at that time was outpatient consultation and care of milder emotional disturbances, with hospitalization in areas of the hospital designed for general medical care. In November 1950 a floor in a wing of the hospital was designated and transformed for care and treatment of psychosomatic cases. With this area set aside for specialized care and treatment, the use of organic therapies was possible.

The medical staff serves for inpatient service as well as outpatient. The nursing staff of the unit consists of the head nurse and her assistant and four general duty nurses. One female practical nurse, a male practical nurse, three nurse attendants and four orderlies assist the nursing staff in the care and general management of hospitalized patients. One occupational therapist devotes her afternoons to instruction and supervision of craft work.

After the opening of the unit in November 1950, medical residents and interns were rotated through the service as part of their training. In July 1951, one assistant resident was obtained for full-time service, along with a full-time senior resident with four years postgraduate training. These additions to the medical staff offered greater opportunity for more supervised therapy. These two physicians continued their services through 1952 and are still active; in addition, one full-time assistant began service on July 1, 1952 and another on March 1, 1953. The American Medical Association has granted approval for two years' postgraduate training in psychiatry to the hospital.

### *Therapy*

Electroshock therapy, insulin and other therapeutic psychiatric tools were utilized to the advantage of the patient and the therapist. In the first year of its operation as a specialized treatment area, 624 patients were admitted to the psychosomatic unit, and approximately 1500 electroshock treatments, 1700 insulin treatments and 500 intravenous ether treatments were given. In the next 12 months there were 770 admissions, 1700 electroshock treatments, 960 intravenous ether treatments and 20 carbon dioxide-oxygen inhalation treatments. During the year ending December 31, 1952, there were 713 admissions, 3,047 electroshock treatments, 1,195 insulin treatments and 612 carbon dioxide-oxygen inhalation treatments.

Other forms of therapy which have proved extremely beneficial are occupational therapy and group therapy. Both of these have been given to inpatient and outpatient groups. Occupational therapy to inpatients is a form of relaxation from daily hospital routine; new interests are stimulated, directing their energies along constructive lines. Certain outpatients have returned to occupational therapy prior to return to actual employment. Here once more they are able to work on a project which serves as an intermediary between the hospitalization period and actual return to work. We know that for many individuals the adjustment period following hospitalization is difficult. By returning as outpatients, they add to their security and feelings of self-accomplishment. This in turn is transferred to their daily work.

Group therapy also has been a regular part of the unit program. The patient in group therapy as an inpatient is in a controlled situation and is allowed to ventilate and verbalize his feelings in front of others also having emotional problems. The group responds, and this constitutes a type of psychotherapy different from that given in an individual interview by the psychiatrist. For outpatients the group problems take on a more realistic trend. However, by presenting all problems in a group situation, the individual benefits by others' experiences and can see his problem to a satisfactory conclusion.

### *Additional Needs*

There is no doubt that the unit as operated so far has met the needs of the community within its limitations. Each member of the team has put forth his best effort to make the venture a success. The unit has demonstrated its effectiveness in offering competent psychiatric service to the community. Certain lacks have become apparent to those who are familiar with its operation:

*1. Medical personnel*—The addition of at least two more full-time trained psychiatrists would be necessary to provide sufficient medical help to meet the demands of the inpatient and outpatient services. One of these could well be a trained child psychiatrist who would devote full time to outpatient treatment of children. Internists and other specialists should be assigned to the unit.

*2. Ancillary staff*—Two more trained psychiatric social workers could devote full time to the inpatient and outpatient services and aid immeasurably in handling patients and families. A full-time psychologist would alleviate the situation somewhat and allow reduction of the part-time psychology staff.

*3. Staff*—The demands of the physicians and the community are such that an increase of the beds to a total of 50 would be necessary to accept, evaluate and to treat all patients referred to the unit for hospitalization

and to reduce still further the number transferred to state hospitals. More office space and separate areas for children, play therapy and group therapy are necessary for the outpatient department, in addition to more waiting room. The rooms available for psychologic testing are inadequate, as is the electro-encephalographic room.

*4. Financial support for indigent patients*—Until November 1952 there was no source of income to the hospital for treatment of the indigent patient; the patient who could not be treated as an outpatient had to be institutionalized. In November the state offered to underwrite two beds per day for indigent patients; this materially reduced the certification rate to state hospital but is inadequate to cover more than a small share of indigent patients.

*5. Convalescent care*—There are patients who could be transferred to a convalescent home if it were adequately supervised and thus saved the expense of hospitalization, and who could be slowly reoriented and reabsorbed by the community, alleviating a necessity for transfer to state hospital under the conditions now existing.

Public relations have been furthered. Many staff members from the Psychosomatic Department have been called on to address various community groups. In general this has been directed along the lines of promoting mental health. The resident has participated in this activity. A more complete understanding of the Psychosomatic Unit and its function in the community has been given to the layman as well as the practicing physician. In addition, a well-organized teaching program is in progress.


***Summary***

The need for a psychosomatic ward in a general hospital has been demonstrated by the pioneer pilot program at the Ellis Hospital. Many services have been offered which heretofore were not available to the community and the general practitioner. There is need for expansion, improvement in facilities offered and changes in the methods applied. Increased space, personnel and budgetary requirements are of principal importance. There is need for more research and objective statistical evaluation of the services offered.



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## THE TRANQUILIZING DRUGS

WHEN William Osler[1] made his valedictory address to the University of Pennsylvania in 1889, he chose the subject "Aequanimitas." He said, "In the physician or surgeon no quality takes rank with imperturbability." Then he defined the word: "Imperturbability means coolness and presence of mind under all circumstances, calmness amid storm, clearness of judgment in moments of grave peril, immobility, impassiveness, or, to use an old and expressive word, *phlegm*." He was doubtful that it could be acquired except by inheritance and he thought that some of his students, "owing to congenital defects," might never be able to acquire it. He counseled, nevertheless, that education with practice and experience might help to attain imperturbability in fair measure.

The doctor, Osler felt, should develop an "inscrutable face by education of his nerve centers." In concluding this discussion of imperturbability he said: "Cultivate then, gentlemen, such a judicious measure of obtuseness as will enable you to meet the exigencies of practice with firmness and courage without, at the same time, hardening the human heart by which we live."

The mental equivalent to imperturbability which Osler called "a bodily endowment," is a calm equanimity. He considered one of the first essentials in securing a good equanimity is "not to expect too much of the people amongst whom you dwell." Osler recognized that prosperity is an aid to equanimity and enables us to bear with composure the misfortunes of our neighbors.

At the most recent meeting of the Society of Biologic Psychiatry, the president, Dr. Harold E. Himwich,[2] said, "A few short years ago it would have been impossible to read a paper on the new tranquilizing drugs, but now we know that chlorpromazine and reserpine are valuable in the treatment of disturbed psychotic patients." Since that paper was read, other drugs have been added to the list, notably FRENQUEL®, MILTOWN® and EQUANIL®. These are the drugs which affect the brain. Both reserpine and chlorpromazine depress the hypothalamic mechanisms, particularly that part concerned with the patterns for emergency, for fight and flight. Chlorpromazine depresses not only these mechanisms but also the sympathetic and parasympathetic nervous systems. Other research has indicated that chlorpromazine prevents the awakening, alerting or arousal reaction producing what is in effect a pharmacologic lobotomy. Frenquel, according to Himwich, depresses neither the hypothalamus nor the activating system and is still a potent tranquilizing drug.

The mechanism by which these drugs have their effect is not clearly established. However, some evidence indicates that a neurohormone called serotonin is involved. When it is insufficient in amount to produce its normal effects, abnormal behavior may be observed. In concluding his address Himwich wrote, "These new drugs are not a flash in the pan, but their therapeutic values have been widely corroborated. However, they are not a complete answer to our therapeutic problem, because no one drug is able to ameliorate the condition of all of the patients and none of them is as efficacious for melancholia as is electric shock."

The discovery of new drugs of this type invariably sets off a chain reaction in which new fields are investigated and various combinations of new and old drugs are tested for specific effects. Already there are combinations of reserpine with various sedative drugs of the barbiturate series and with other active ingredients. In one study reserpine and chlorpromazine were given in combination and the combination was said to have certain advantages over therapy with reserpine alone. Indeed, the authors say that chlorpromazine seemed to potentiate the clinical effects of reserpine. "The course of combined therapy," say Drs. J. A. Barsa and N. S. Kline,[3] "was less stormy and less distressing to the patient because of the milder and shorter turbulent period." Already these drugs are said to have worked miracles in state institutions for the mentally disturbed, permitting great numbers of patients to be discharged to their homes beyond what might have been possible in previous years. Dr. A. E. Bennett[4] says that "both drugs have facilitated psychotherapy through physiologic relief of anxiety, tension, insomnia or somatic symptoms in some cases."

In addition to the drugs already mentioned, consideration must be given to the pharmacologic properties of Miltown which is a meprobamate, a drug which is related to mephenesin and which was found in a study of such preparations to be the most potent anticonvulsant in the series and also to possess a muscle-relaxant action of considerable intensity and long duration. Dr. J. C. Borrus[5] found that it was most effective in anxiety and tension states through a lessening of tension, reduced irritability and restlessness, more restful sleep, and generalized muscle relaxation. Chiefly in its favor is an absence of toxicity both subjectively and objectively as compared with other drugs, and "there were no withdrawal phenomena noted on cessation of therapy." Dr. Lowell S. Selling[6] confirmed its nonhabit-forming character and found it of most value in the so-called anxiety neurosis syndrome, especially when the primary symptom is tension. His studies and other studies made since his first publication indicated a special value to Miltown in accomplishing withdrawal from alcohol with a minimum of discomfort. Among the special qualities listed for this drug, based on clinical studies, are as an agent in anxiety and tension states; as a muscle relaxant, particularly in fibrositic rheumatic disorders; an agent in such conditions as torticollis and back pain; for control of spasticity in such conditions as cerebral palsy, and as a somnifacient of a different order than the hypnotics or sedatives. Few allergic reactions have been reported and all of them responded to therapy with antihistamines. In a new series of studies by Dr. F. Lemere[7] this drug proved effective in 70 per cent of a group of 250 nonhospitalized patients and he considers it "the drug of choice for the relief of tension, anxiety and insomnia."

Another discovery has reported this drug selectively effective in a high percentage of cases of petit mal. Further, several reports by general practitioners have indicated its desirability in what are commonly called tension states but which might include psychoses, psychoneuroses and personality disorders, as well as a wide variety of conditions classified en masse as psychosomatic, including headaches, dysmenorrhea, hypertension, motion sickness, peptic ulcers and a variety of dermatologic disorders.

One wonders what Sir William Osler might have said had he had available in 1889 such aids to imperturbability and equanimity as have come with the new tranquilizing drugs. This is in the nature of a medical revolution. Ten years hence statistics of institutions for

the mentally disturbed and for the alcoholic may indicate the results of administration of these and other new remedies which are bound to come. Already the great progress that has been made is an indication of the future.

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## MENTAL ATTITUDES OF MEDICAL WORKERS

In Great Britain during the first week in March, 10,000 nurses associated with 33 mental hospitals declared that they would no longer work overtime. This method was chosen to express their dissatisfaction with their pay and conditions of their work. According to the London *Lancet*, longer and longer hours are demanded of a dwindling staff who are not paid extra when they come early or stay late. Hospitals of Great Britain are suffering unduly from a shortage of nursing personnel. The management committees of the hospitals generally in Great Britain are becoming uneasy at their inability to offer hospital workers rates of pay having reasonable relationship to what is paid by factories or airports. The *Lancet* comments:

> We note with deepening anxiety the tendency of people in the health service to adopt the mental attitudes and techniques of organised labour, which are often irreconcilable with those of a profession. But in this case, as so often in industry, part of the responsibility for direct action lies with those who tend to delay necessary concessions until these are made urgent by a threat.

American physicians and hospital administrators will remember that when the British Parliament proposed to take over the medical profession and the hospitals as a governmental function, the prediction was generally made that the attitudes usually associated with employment under such circumstances would soon prevail throughout Great Britain. Not many years have passed since the new methods began to function but here already is the evidence that the total administration of medicine as a government function is incompatible with the professional quality of the service.

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## AMERICAN-KOREAN FOUNDATION

In 1954, 1,336 American physicians gave $20.00 each to pay for 2,095 "Korean Doctors' Suit Packages," each of which contained enough good wool cloth and findings for two suits and a plastic raincoat.

This type of practical philanthropy is so impressive for the good that it can do in human relations that the record is worth remembering. Some of the accomplishments of the American-Korean Foundation toward the improvement of medical and health services in Korea during the last two years are also worthy of note:

1. Over 200 Korean physicians, medical educators, dentists and other health workers have been assisted by the AKF to come to the United States for advanced training.

2. Each medical, dental and nursing school in Korea has received financial aid and equipment from the American-Korean Foundation.

3. Medical and health supplies, drugs and equipment, contributed by American industry and individuals, valued at over $3,000,000, have been sent to Korea.

4. Funds totaling over $700,000 have been allocated to specific medical and health projects in Korea.

The medical schools in Korea are beginning to approach a scientific efficiency which will help them answer the problems of Korean health in the years to come. American physi-

cians who have participated in this type of work may well be very proud of the accomplishments.

MORRIS FISHBEIN

## HOSPITALS AND THE PRESS

UNDER auspices of the British Medical Association, with Dr. H. Guy Dain as chairman, a conference of doctors and press organizations was held in London to establish a guide for both hospital authorities and press representatives for issuing news about hospital patients. Eight recommendations were adopted which seem apropos in solving problems that confront hospital authorities everywhere, and which are of concern to doctors and patients also. The custom has developed in cases of illness of noted persons for physicians, either singly or in groups, to issue bulletins at regular intervals to the press associations. Difficulties arise, however, in such cases at the birth of a baby with two heads, Siamese twins, babies weighing less than 2 and more than 25 lb., and patients who are injured in automobile, railroad and airplane accidents. The British statement takes account of all such contingencies and may well serve as a model in the United States. The recommendations are:

### *Sickness Cases*

1. No information should be divulged to the press without the consent of the patient, beyond the admission on inquiry that the person concerned is a patient. Where, however, even this statement would be deleterious to the patient's interests, his presence in the hospital should not be disclosed without his consent. For example, in certain special hospitals, such as mental hospitals and sanatoria, where the mere admission of the patient implies the nature of the diagnosis, no information should be given to the press without his consent.

2. In the case of well-known people (and subject always to the patient's consent) a brief indication of progress may be given, in terms authorized by the doctor in charge.

3. In the circumstances referred to under (1) and (2), where the patient is too ill to give his consent, or is a minor, the consent of the nearest competent relative may be accepted.

### *Accident Cases*

4. *(a) Individual cases*—The press should be given, on inquiry only, and at the time of the inquiry or as soon as possible afterward, the name and address of the patient and a general indication of his condition. The patient's relatives should normally be informed before any statement is given to the press; but if it has not been possible to do so, this should be made clear to the press. Further information should be given only with consent.

*(b) Multiple cases*—In accidents involving a number of people (for example, a railway or air accident) all reasonable steps should be taken to inform relatives of the injured before the publication of names, bearing in mind the necessity of early publication to dispel the anxiety of the next of kin of all other persons who were, or might have been, involved in the accident. Further information should be given only with the patient's consent.

5. Hospitals admitting accident cases should maintain a casualty book by reference to which inquiries may be answered.

### *General*

6. All hospitals should ensure that a sufficiently senior and responsible officer of the hospital is at all times available, whether in person or by telephone, to answer press inquiries, and should nominate an officer or officers for this purpose.

7. When dealing with press representatives who call at hospitals and are unknown to them, such hospital officers are advised to ask to see evidence of accreditation in the form of a document issued by the press representative's newspaper, news agency, or photographic news agency, or a membership card of the Institute of Journalists or National Journalists Union.

8. Cooperation between hospitals and the press must depend on mutual confidence and good personal relations. Difficulties and misunderstandings should be taken up between the hospitals or board concerned and the local press.

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